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財団法人 日中医学協会
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研究室で撮影した本人のスナップ写真、及び発表論文のコピーを添付

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  研究テーマ __胃がん予防に関する生活習慣要因__

2. 本年度の研究業績

  (1) 学会・研究会等においての口頭発表　　有　・　(無)　（学会名・内容）

  (2) 学会誌等に発表した論文　　(有)・　無　（雑誌名・論文名）

  International Journal of Cancer

  Comparison of lifestyle and risk factors among Japanese
  with or without a gastric cancer family history

３．今後の研究計画

今後の研究テーマ：大腸腫瘍摘除後の再発予防に対する食生活介入試験

計画：これまでに某大学で大腸腫瘍摘除を受けた患者を対象にして、臨床試験への参加のインフォームドコンセントを入手し、無作為に実験群・対照群に割付を行い、大腸腫瘍再発予防のための食習慣変容と健康食品摂取介入を実施している。すなわち、対照群には総脂肪摂取を抑制し、実験群には総脂肪摂取の抑制に加えて、1) n－6 多価不飽和脂肪酸（PUFA）摂取抑制、2) n－3 PUFA 摂取勧奨の勧奨を行い、n－6 PUFA/n－3 PUFA 比を 4~5 から 2~2.5 へ下げることを目標とする。2~3 年後の腫瘍再発をエンドポイントとして、実験群と対照群の間の発生率を比較する。定期的に食生活調査・健康食品摂取調査および血中脂肪酸や抗酸化物質の分析を行って、コンプライアンスをチェックする。本年度中に症例群 100 人、対照群 100 人のエントリーを目指す。

４．研究指導者の意見

　　昨年、貴財団からご支援をいただき、黄君は研究に専念することができました。すでに「家族暦以外の胃がん危険因子における比較分析」という論文を国際学術雑誌に報告した、さらに「胃がん予後に関する生活習慣要因」という論文も投稿中であります。

　　私費留学生の黄君にとって、貴財団からの経済的援助は非常に有り難くかったものと信じます。

　　今回の貴財団のご支援を心から感謝致します。

<div align="right">研究指導者氏名　　　　　　　　　　㊞</div>

５．研究報告

　　別紙形式を参考に、報告本文4000字以上で報告して下さい（枚数自由・ワープロ使用）

　　タイトル・要旨等は日本語で、KEY WORDS以下は日本語或いは英語で記入して下さい。

　　研究成果の発表予定がある場合は発表原稿・抄録集等を添付して下さい。

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研究テーマ
生活習慣と胃がんの予防

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要旨（日本語）

　　胃がん家族歴のあるなしにかかわらず胃がんの特定の危険因子を発見するために、同時に 2つの分析疫学研究が行われた。まず、胃がん外来患者と非癌外来患者に対して胃がん家族歴のあるなし、それぞれの行動・生活習慣を比較した。胃がん家族歴のある人はない人より初診に消化器科を受診、又は胃がん検診を受ける割合が統計学的有意に高く、一方、飲酒・喫煙及び大部分な食生活習慣は統計学的差が示されなかった。さらに、全外来患者を胃がん家族歴のあるなしの二群に分けて、それぞれの症例・対照研究を行った。2 つの症例・対照研究で同時に、消化器科を初診療科として選択した場合と飲酒・喫煙場合はオッズが統計学的有意に増加し、自分の意志で受診した場合と頻繁に生野菜と人参を摂取する場合はオッズが減少する。 2 つの症例・対照研究から得た危険因子は顕著的な差がなく、したがって、胃がんの予防対策は胃がん家族歴のあるなしにかかわらず同様の方法で推進することが示唆された。

KEY WORDS

生活習慣、胃がん

研究報告

目的
↓
方法
↓
結果
↓
考察
↓
参考文献

研究報告

目的 :

Although it is gradually clarified that dietary, drinking and smoking habits attribute to the onset of gastric cancer, little is known whether the prognosis of gastric cancer is also associated with these factors. In order to examine this hypothesis, a prognostic analysis was conducted by using data from Aichi Cancer Center Research Institute and Hospital.

方法 :

From January 1988 to December 1994, information of 877 gastric cancer patients (578 male, 299 female) regarding habitual smoking and drinking, food consumption, histological grade and clinical stage of tumor, as well as follow-up results was collected. Survival statuses of all patients were followed up till December 1998. The survival function was estimated by the Kaplan-Meier method. Proportional hazard analysis was used to test the effect of each lifestyle item on gastric cancer death.

結果 :

After controlling age, gender, histological grade and stage of disease, hazard ratios were calculated. The ratios of consuming raw vegetables (0.74, 95% CI: 0.56-0.98), tofu (0.65, 95% CI: 0.42-0.99) and chicken meat (0.61, 95% CI: 0.39-0.95) for more than 3 times/week were significantly decreased. However, the risk ratio were 2.53 (95% CI=1.22-5.29) for habitual smokers, an inverse dose-response relationship was also found between ever smoking and gastric cancer patients' survival. Therefore, It was suggested from this study that frequent intake of raw vegetables and tofu were favorable, while habitual smoking was a risk prognostic factor for gastric cancer.

考察 :

Because dietary, drinking and smoking habits were well known as cancer risks, it was reasonable to postulate that these factors also could affect the progression of cancer. Over the

past two decades, studies on cancer prognosis and these lifestyle factors had been conducted, but mainly focused on cancer of breast (10-26), laryngeal (27), lung (28), oral (26,29), as well as malignant epithelial tumors in the upper digestive tract (30). These results convinced that frequent intake of vegetable and fruit were favorable, while habitual smoking and high-fat diet was a harmful prognostic factor, which was consistent with most etiological investigations. But few analyses concerned the lifestyle determinant on the prognosis of gastric cancer. Perhaps there were unexpected difficulties or a technical limitation in performing this kind of studies on gastric cancer.

First might be the inability to characterize antineoplastic treatment with any greater detail than surgery, radiation therapy, chemotherapy, or combined therapy. But it seemed very unlikely that a lack of these variables biased the main results, because practical choice of treatment was overwhelmingly based on clinical stage of tumor. To avoid statistical over adjustment, it was a proper choice to put only tumor stage, rather than two strongly related variables simultaneously into Cox regression model. Moreover, radical gastrectomy remained the only chance of cure for early staged gastric cancer, different adjuvant chemotherapy had not been presenting prognostic benefits by controlled clinical trials (31). Due to the same reason, few of our cases received adjuvant chemotherapy after radical gastrectomy. For later stage, high-dose 5-fluorouracil (5-FU) was still a key regimen that serving as the basis of third generation chemotherapy, but the effect still confines to palliation; the long-term survival result remained unsatisfactory (32). In terms of radiotherapy, which was not a routine choice for gastric adenocarcinoma in ACCH, no cases received this treatment, so it would not bias our calculations.

Second might be a lack of later information on lifestyle. All lifestyle information was collected before cancer diagnoses in order to keep recall bias lower, so it was not known if or

how the dietary habits would have been changed afterwards. Although most of our cases were more than 50, their dietary habits did not tend to be changed, it was reasonable to postulate that part of cases would stop smoking or limit their tobacco consumption after the diagnosis of gastric cancer. Thus, it was possible that the amount of tobacco smoked had been estimated imprecisely. This might cause an underestimated risk. Under this consideration, we must put an indispensable premise in our study: dietary habits prior to the diagnosis of gastric cancer, to avoid conceptual misleading.

Cases in our study mostly came from Chubu district of Japan. Their overall survival was comparable to those in other area of Japan (33), however obviously better than reports from European or American studies (34). Some researches suggested that relatively younger aged patients, the unique early diagnostic system and wide conduction of N2, N3 tumor resection caused this survival difference (35). The high resection rate would lead to longer life span of the case series. This might cause a bias, considering that no habitual smoking or frequent intake of raw vegetables might contribute to decreased death rate from other chronic diseases. So, to avoid affecting the main results, events from non-cancer deaths was excluded from this study.

After taking into account the relevant role of clinical and pathological factors, one of the major findings of this study was that, habitual smoking had prognostic significance on gastric cancer patient's survival. An attempt to explain this observed difference might involve the effect of cigarette smoking on immune system. Cigarette smoking was believed to correlate with unhealthy nutritional intake (36), causing immunosuppression and impairment of patient's ability to destroy cancer cells. Long-term tobacco exposure studies also indicated that immunosuppressive would develop (37): decreased lymphocyte proliferation in response to the mitogens (PHA or LPS) (38), and T cell anergy (39) suggested compromise of cell function; antibody production could also be suppressed caused

a fall of IgA, IgG, IgM and lysozyme concentrations (40).

A cohort study from Japan indicated that a dose-response relationship existed between cigarette smoking and mortality rate of pancreatic cancer (41). But the association with gastric cancer was not revealed in a prognostic study conducted in the United States (26).

In this study, frequent intake of raw vegetables was suggested with improved survival of gastric cancer, by both survival function test and proportional hazard analysis. It could not be denied that frequent intake of vegetables or fruit is correlated with high socialeconomical status, which was a favorable prognostic factor for gastric cancer (7). However, there is no tremendous rich-poor gap in Japan, the majority of Japanese are well-known middle-class. We believed this would not confuse our main results.

It has been proved that micronutrients with bioactivity are abundant in raw vegetables including carotenoids, vitamin C, dietary fiber, vitamin E and selenium. Experimental systems containing these micronutrients appeared to be able to reduce DNA damage and mutagenesis (42). Besides of the direct anti-cancer effects, these micronutrients also reinforced the immunological function, e.g. carotenoids had been shown to influence immune responsiveness through enhancement of T and B lymphocyte proliferation and improvement of cellular communication (43). Increased immunocompetence would decrease the likelihood of complications and death due to infectious agents.

Most interesting finding in this study was the effect of frequent intake of tofu on decreased HR for gastric cancer death. Etiological researches suggested that frequent consumption of soy products might contribute to the relatively low rates of breast, colon, and prostate cancers in China and Japan (44). Besides this, Japanese (2) and Korean (45) study also showed decreased risk of tofu for gastric cancer. One biologically plausible explanation was that soybean products provided a unique dietary source of isoflavone including genistein.

Isoflavone exhibited a number of anti-metastasis activities, including a specific inhibition of DNA topoisomerases (46-47) and protein tyrosine kinases (48-49), regulation of cell cycle progression (50), inhibition of cell proliferation (51-52), antiangiogenic activity (53) and inducement of apoptosis (54-55). Recent *vivo* mice test revealed that dietary supplementation of soybean protein isolate reduced pulmonary metastasis of B16BL6 cells and inhibited the growth of tumors that developed in lung (56).

From our results, difficult to interpret was the protective effect by meat, especially chicken meat. This might be tentatively considered as a surrogate of a good nutritional status. With the same reason, a protective effect of meat had also been found in esophageal cancer (57) and laryngeal cancer (27).

In conclusion, the present study suggested that dietary, drinking and smoking habits prior to the diagnosis played an important role in the prognosis of gastric cancer; frequent consumption of raw vegetable or tofu before diagnosis was a favorable, while habitual smoking was a harmful prognostic factor for gastric cancer. A potential way of improving gastric cancer survival might be achieved by a proper modification of lifestyle.

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