

者たちと綿密に打ち合わせながら、研究基盤をつくらねばならない。

E. 結論

アジアは、癌の急増地帯であるものの、医療格差が大きく、文化的多様性に満ちていて、統一した対策がとりにくい地域である。癌は、医学のみならず、それぞれの地域の政治、経済、文化など様々な社会的要因に左右される病気である。それゆえ、がんへの疾病観は、地域により異なることも予想される。これまでいくつかのアジアにおける疫学研究は行われてきてはいるが、その背景にある人々の暮らしの中で捉えた、がんへの意識調査の地域比較は行われていない。世界的疾病構造の変容の中で、アジアがんフォーラムは、Cross-boundary Cancer Studies として大学における学際的研究及び教育プログラムを立ち上げ、日中韓の国際連携プロジェクトの準備を進めている。この Cross-boundary Cancer Studies に基づいて、がんに対するアジア意識調査を行うことによって、がんに対する地域ごとのとらえ方の相違点・共通点を見出し、それぞれの地域ごとの癌に関する人々の意識のバロメーターを作成することを今後は目指すべきではと考える。それが、日々の生活習慣や地域的な風土などを結びつけたがんの予防・治療への反映されることで、癌の急増地域であるアジアのがんの克服に貢献できる。行動変容は環境を変えると起こりやすいといわれているが、それぞれの地域社会での取り組みに反映できる指標を探す必要がある。今後、最新の behavior science も用いてこの結果を用いて、アジアがん

バロメーターとしての、調査課題の設定や対象者の抽出方法など、課題を考察していかねばならない。

F. 健康危険情報

(総括研究報告書にまとめて記入)

G. 研究発表

1. 論文発表

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H. 知的財産権の出願・登録状況

(予定を含む)

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

参考資料

The 9th Asia Cancer Forum
Cross-boundary Cancer Studies
September 19, 2012

AGENDA

Moderators: Hideyuki Akaza, Norie Kawahara, Tohru Masui

1. Setting the Issues

Based on discussions at the 8th Asia Cancer Forum

Discussion points and challenges for the Asia Cancer Forum to date

Hideyuki Akaza, Professor, RCAST, The University of Tokyo

Pursuing global actions for conquering cancer by collaboration between Russia and Japan (Report from the Japan-Russia Far East Forum 2012 (pre-APEC meeting))

Akira Nakagawara

President of Chiba Cancer Center

Cross-boundary Cancer Studies

Norie Kawahara, Organizer, Asia Cancer Forum,

Assistant Professor, RCAST, The University of Tokyo

Asia High Technology Network: Quest for Excellent Brains

Jun Miyake, Professor, Graduate School of Engineering Science, Osaka University

2. Looking Beyond Specialist Areas to Understand Contemporary Issues for Cancer in Asia: Starting from Multi-disciplinary International Cancer Studies

Masafumi Nogimori, Representative Director and Chairman, Astellas Pharma Inc.

Masui Tohru

Department Director, National Institute of Biomedical Innovation

3. Our Challenges: Possibilities for and Issues Relating to Trilateral of Cross-boundary Cancer Studies

Jae Kyung Roh, Professor, Yonsei University College of Medicine

Haruhiko Sugimura, Professor and Chairman, Hamamatsu University School of Medicine

4. Discussion

Discussants:

5. Peter Wushou Chang, Vice Dean, College of Public Health & Nutrition, Taipei Medical University

6. Shigeo Horie, Professor and Chairman, Department of Urology, Teikyo University

7. Manami Inoue, Section Head, Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center

8. Tomoyuki Kitagawa, Institute Director Emeritus, Japanese Foundation for Cancer Research

9. Yumiko Mochizuki-Kobayashi, Division Chief, Tobacco Policy Research, National Cancer Center

10. Park Eun-Cheol, Dept. of Preventive Medicine, Institute for Health Services Research, Yonsei University College of Medicine

11. Kazuo Tajima, Director, Aichi Cancer Center Research Institute

SUMMARY OF MEETING

OPENING

Norie Kawahara, Research Center for Advanced Science and Technology (RCAST), The University of Tokyo and organizer of the 9th Asia Cancer Forum began by welcoming participants. She noted that in order to explain the efforts to date of the Asia Cancer Forum a short booklet had been distributed to participants. She also noted that during the meeting the participants at the Asia Cancer Forum would seek

to further advance discussions and initiatives on cancer control and treatment in Asia.

1. Setting the Issues

Based on discussions at the 8th Asia Cancer Forum: Discussion points and challenges for the Asia Cancer Forum to date

Hideyuki Akaza, RCAST, The University of Tokyo, noted that one of the priority issues for the Asian health agenda is the super-aged society. In recent years the change in disease-specific priorities has gradually shifted from infectious disease, to babies and infants, then to metabolic syndrome and finally cancer. To date the Asia Cancer Forum has focused its discussions on the critical importance of placing cancer on the global health agenda as a means of promoting global action. The Asia Cancer Forum has also undertaken to:

1. continue to conduct research among experts on their perceptions of the current situation concerning position of cancer on the global health agenda, seeking to share a common philosophy on global health and enhance cooperation in the field of global health;
2. create a new approach by proposing lifestyle changes aimed at preventing cancer that take into consideration historical and cultural diversity;
3. actively provide scientific and technological assistance that enable clinical trial to be conducted in both industrialized and developing countries and aim to act as a bridge between the industrialized and developing world in the field of cancer research;
4. seek to create multidisciplinary education program that combines humanities and sciences

and launch Global Collaborative Cancer Studies for the purpose of overcoming health disparities among different countries and regions and building mutually complementary long-term partnerships (the Japan-Asian Studies Program at the University of Tokyo is one example of such a multidisciplinary educational program); and

5. encourage cooperation and collaboration among Asian federations that are engaged in efforts to deal with cancer issues.

With regard to the various disciplines that are involved in handling cancer issues, one of the challenges that are faced is that activities are mainly done independently of each other, including basic research, clinical research, patient advocacy and regulatory science, among others. The aim of the Asia Cancer Forum is to combine all these various sectors and fields and engage in cross-boundary cancer studies that will identify new ways to cooperate and show a way forward for regional joint efforts.

Pursuing the global actions for conquering cancer by collaboration between Russia and Japan (Report from the Japan-Russia Far East Forum 2012 (pre-APEC meeting))

Akira Nakagawara, Chiba Cancer Center, reported that the Japan-Russia Far East Forum 2012 was held as a pre-APEC meeting in Vladivostok in September. The main theme of the meeting was a collaborative network for cancer. The items discussed had included the following:

1. Current status of cancer medicine and research in Russia and Japan
2. How to solve the current programs of pediatric oncology in Russia and Japan
3. How to organize the transition from childhood to adult cancer

4. Collaborative projects to solve the problems of Chernobyl and Fukushima

5. Future collaborations for childhood and adult cancers between Russia and Japan

6. Proposals of the joint project between Russia and Japan

7. Pursuing the global actions for cancer by collaboration between Russia and Japan.

Q&A

Shigeo Horie, Department of Urology, Teikyo University noted that it was meaningful to hold the Asia Cancer Forum with the ultimate aim of uniting Asia in endeavors towards cancer control and treatment. He also noted that cancer is a great threat to patients in that it presents the specter of imminent death, in contrast to other disorders and diseases that are more readily curable. He stressed that it is important to deal with cancer in a quantitative manner in order to present the public with figures that are convincing, thereby generating greater support and understanding for cancer care, control and treatment efforts.

Manami Inoue, Research Center for Cancer Prevention and Screening, National Cancer Center, noted that she had engaged in discussions in the Asia Cancer Forum on several occasions and stressed the importance of collaboration not only with medical scientists, but also with economic scientists, given the severe economic challenge that cancer presents to all countries. She noted that there is a severe lack of information concerning the economic burden presented by cancer and commended Park Eun-Cheol, Dept. of Preventive Medicine, Institute for Health Services Research, Yonsei University College of Medicine for his presentation in the previous UICC

International Session concerning the economic burden of cancer in Korea. She stressed that an initiative to implement cross-boundary cancer studies could be instrumental in expanding research in various areas. Peter Chang, College of Public Health & Nutrition, Taipei Medical University, noted that one of the areas to look at is the position of patients in society. It is important to assess the burden on the patient, family, community and company, etc. In the context of the Social Determinants of Health as defined by the World Health Organization (WHO), there are various vectors that require consideration from a cancer perspective. An Asian-wide effort to improve the quality of cancer control and treatment is an urgent challenge.

Cross-boundary Cancer Studies

Norie Kawahara, RCAST, The University of Tokyo, noted that the Asia Cancer Forum has engaged in discussions to date from multiple perspectives, with the aim of raising awareness of cancer on the global health agenda. Cancer research to date has tended to be intensive and segmentalized, making it easy to lose sight of the bigger picture. Keeping the big picture in mind could help stakeholders to create a blueprint for the future direction of cancer research. When discussing the challenges that lie ahead it is essential to consider the characteristics of cancer treatment. The question of why cancer has not been given its proper position in the framework of international healthcare must also be addressed.

It is essential to bear in mind that we are now in the early stages of what should become a global healthcare movement. There are many actions and initiatives that aim to couple healthcare with development challenges. However, there are still many people who question whether cancer can logically be included in

the linkage between healthcare and development. This is because the logic of global health is heavily influenced by political dynamics in the international community, centering on the U.S. and Europe. However, the Asian health agenda is different. Cancer in Asia is characterized by the following: It is greatly influenced by the aging of society; it also has significant social components; and it is also one of the most difficult diseases to treat, because there is no uniform treatment.

We have now reached a crucial point for cancer in Asia. In order to overcome the confusion and lack of consistency in our approach to cancer, it is essential to create a platform for discussion. This platform should not be just for Japan, but rather it should be international in nature. It needs to join the countries and people of the region in considering the way forward for cancer issues in Asia. Separate from the actions of the cancer research and advocacy communities, we need to form a multidisciplinary academic platform. This platform should be capable of perceiving cancer through a holistic approach.

Universities share universal values and are international institutions. They have the potential and academic resources to create a multidisciplinary platform that embraces both sciences and humanities. The "Cross-boundary Cancer Studies" program was established by the University of Tokyo for the following purposes:

1. Define the meaning of "cross-boundary studies" and develop a concept that can overcome the confusion that currently exists;
2. Establish year-round cross-department lectures and seminars in universities in Japan, Korea and China;
3. Standardize curriculum and skills; and
4. Coordinate with other projects in the field of global

health.

These efforts are aimed at tackling one of the biggest challenges for the field of cancer, namely gaining political momentum and creating an upsurge of political support.

The Cross-boundary Cancer Studies program is based on the resources of the Asia Cancer Forum and its members. This year marks the second year of the program. The program seeks to formulate a contemporary image of Asia from the standpoint of cancer. Issues that the program covers include: the disjoint between globalism and nationalism in Asia, the diversity of views about life and death, and social justice. The program also asks why the inconsistencies in Asia are different from the ideal vision of global health. One of the reasons for this is that cancer medicine and treatment is viewed in the context of national interests. Competition in pharmaceutical development is also intensifying, presenting complex challenges for regulation and open-access.

Vice President of the University of Tokyo, Prof. Shunya Yoshimi has previously noted that in order to create new knowledge from multidisciplinary education, it is essential to create a platform to ask the question "What is knowledge in the university context?" Specialist knowledge alone will not be sufficient to create new knowledge. In order to achieve a paradigm shift and create a vision of the future based on the current complex reality, freedom and liberalization of knowledge is required. Prof. Yoshimi has also noted that a university is a form of "media," and it must create multiple streams of education and learning. In a world in which society is becoming more mobile and interconnected there is the potential to change learning and knowledge structures from their previously defined norms.

The Cross-boundary Cancer Studies program aims to invite external lecturers who are preeminent in their particular fields to give omnibus-style presentations in Japan, China and Korea. They will address cancer as multidisciplinary topic and discuss the situations in each of the three countries from the perspective of cancer. The speakers will not only be from a scientific background, but will also include political, economic and cultural experts.

The various analyses implemented up to now by the Asia Cancer Forum will be utilized as a resource to share knowledge on the various themes between Japan, China and Korea. Participating students will not only be medical students, but will comprise a cross-faculty, cross-departmental body from various specialties.

Currently there are various U.S. and European institutions that are establishing centers of learning in Asia and the flow of overseas students to Asia continues. Asian students are also going to study in the U.S. and Europe in large numbers. In order to be able to send out a message from Asia to the world about the distinctive and unique aspects of our society, it is essential to establish an academic platform that will address the differences and commonalities that exist in Asia.

Future challenges can be summarized in three points, as shown on the slide.

The first is the necessity to ensure stable funding for cross-boundary studies. This will require efforts by universities that are organizing cross-boundary studies to find external funding. It will also be important to make sure that these funds remain in place to ensure that programs can continue to run.

The second challenge is to find appropriate human resources who have the required skills. Because the cross-boundary cancer studies program is multi-disciplinary, it will therefore be important to decide the skills that are required. People hired will expect to have a career path and thought needs to be given to how they could develop their skills.

The third challenge is to promote further interaction between universities. Universities already have various exchange agreements in place and run exchange programs for their students. Existing exchange agreements could be used to promote cross-boundary cancer studies, and new cancer research-specific arrangements should also be developed. If an international research and exchange program can be arranged, an evaluation structure will also need to be established, with specific research targets.

These three challenges are inter-connected. For example, if an exchange agreement was in place, it may be easier to secure external funding. Also, if skilled personnel could take the lead in promoting cross-boundary cancer studies, this could be useful for promoting funding and exchange programs.

It will be important to consider how we can address these challenges in a consistent and targeted manner in the future.

Q&A

Yumiko Mochizuki-Kobayashi, Tobacco Policy Research, National Cancer Center noted that for some cultures and countries cancer can be a reason for ostracism. There is a wide spectrum of development stages in the Asian region and it may be useful to engage in specific cultural and social studies regarding cancer. She noted that in the past cancer was regarded

as a stigma in Japan too, but this is largely a thing of the past. The means of overcoming ostracism is an important issue for further discussion.

Kazuo Tajima, Director, Aichi Cancer Center Research Institute noted that the situation in Japan, Korea and China is slightly different to the situation in other Asian regions. Cost-effective measures need to be developed for the Asian region as a whole. In Japan one in five people will experience cancer and therefore cancer treatment is very important. Poverty is also a cause of cancer and correlates strongly to the treatment that is received or available in different countries. Recently the UICC has focused on the control of cancer and promotion of education about cancer prevention. Palliative care is also an important consideration. To date the Asia Cancer Forum has only discussed general issues and it is perhaps time to further focus and hone down the various issues that require greater attention. Dr. Tajima also noted that the health insurance systems and structures in the countries of Asia had not been addressed in the previous discussions of the Asia Cancer Forum.

Jun Miyake, Graduate School of Engineering Science, Osaka University, suggested that it may be useful to work also in cooperation with Taiwan in addition to China, noting that China's size and regional disparities makes it like several countries rather than a single uniform country with a uniform health system.

Haruhiko Sugimura, Hamamatsu University School of Medicine noted that research on intervention and prevention has never been sufficiently addressed and could be raised once again by the Asia Cancer Forum.

Asia High Technology Network: Quest for Excellent Brains

Jun Miyake, Graduate School of Engineering Science,

Osaka University began by noting that he would like to consider the economic basis for cancer control and treatment. The Asia Cancer Forum has been developed as one of the branches of the Asia High Technology Network and has proved to be one of the network's success stories.

The next-generation of successful business in an increasingly interconnect world is likely to be dependent on a large number of "excellencies," rather than a workforce composed of loyal workers. The importance of the value of intelligence is still not fully understood and those who have grasped its significance have proven that intelligence and information lead to success and profitability.

In terms of medical technologies, genome medicine still has a low efficiency. There have been few genome medicines that have been approved. It will be necessary to have much more knowledge in order to fully understand the human body.

One of the questions that should be asked also is what is the next-generation technology? Human interface devices are gaining greater and greater value. These interfaces reflect their cultural backgrounds.

The Ministry of Economy, Trade and Industry of Japan has formulated a Creative Industries Policy in 2010. This is based on the need to create knowledge and innovation. Soft power has now surpassed hard power in its potential. During the 20th century the value of intelligence was small, with the substantial value being prioritized. In the 21st century the reverse is true. Bringing together intellectual and intelligence excellence will be the progenitor of innovation in the modern world.

New technology and science need more and more excellent brains. American success, such as that enjoyed by Apple, shows a large-scale fusion of

business, technology and design. The question is whether a single country in Asia could supply enough talent to be competitive in terms of soft power. The response is that there is a real and pressing need for the Asian region to combine its talent, creativity and knowledge base through full-fledged cooperation.

Q&A

Hideyuki Akaza, RCAST, The University of Tokyo asked what in the modern medical age is the greatest soft power. Jun Miyake responded that organization is perhaps the greatest power. It will be essential for Japan, China and Korea to create an organization for cooperation and to build from that platform.

Jae Kyung Roh, Yonsei University College of Medicine addressed the point about creating an organization and structures for facilitating cooperation in Asia. He noted that at Yonsei University, where there is a main campus and a medical campus, it is possible for all disciplines to interact and communicate together. This has been instrumental in creating a discussion on the social aspects of cancer. Trilateral, cross-boundary cancer studies are therefore essential as a means of promoting cooperation. The initial moves to initiate such a program may be fraught with difficulty, but it is something that must be accomplished.

2. Looking Beyond Specialist Areas to Understand Contemporary Issues for Cancer in Asia: Starting from Multi-disciplinary International Cancer Studies

3. Our Challenges: Possibilities for and Issues Relating to Trilateral of Cross-boundary Cancer Studies

4. Discussion

Masafumi Nogimori, Astellas Pharma Inc., noted that he had been greatly impressed by the enthusiasm of the students during his visits to the University of

Tokyo to act as a visiting speaker in the Cross-Boundary Cancer Studies program. The outside world is changing very quickly and all of society needs to find response measures. Cross-boundary discussions among students at the University of Tokyo has shown that bringing different specialties together can reap results. The structure of the Cross-boundary Cancer Studies program could then be copied in other countries and the resulting programs could be linked together in a cooperative efforts.

From a pharmaceutical point of view, the pharmaceutical companies are constantly seeking to achieve a "miracle drug," and will never stop efforts to develop new drugs and treatments. The knowledge amassed by multidisciplinary, international collaboration would undoubtedly help such efforts in the long term.

Jae Kyung Roh, Yonsei University College of Medicine noted that the concept for Japan-Korea-China cooperative efforts is an ideal one, given that East Asia is the most overall developed part of the Asian continent. It is essential that the three countries take the lead. In the 1990s it was the case that the United States was the unipolar super power. However, the world continues to change, with China now the second-largest economy in the world, with economic union in European having created a European trading group, and other groupings and regions, such as Africa, starting to emerge. It is the case that the Asian mindset is different in cultural terms from the West and other regions, and therefore it is important for Asian nations to come together to engage in cooperation. It may be difficult, however, for one institution in China to be representative of the entire country. Targeted therapy is simply too expensive for some areas of Asia and it is necessary to engage in the

formulation of a cost-effective treatment model that could be realistically applied to all countries in Asia. Gradual and steady efforts towards the realization of regional cooperation must be tenaciously promoted.

Peter Chang, Taipei Medical University, noted that Taiwan is also very interested in research and training, citing the fact that students of his university are required to engage in overseas study and training and that they would be eager to engage in study with other students from Asian countries.

Haruhiko Sugimura, Hamamatsu University School of Medicine gave his perspective from the field of pathology. He noted that the Japanese style of oncology has developed in a unique way. Likewise, the medical practices in central China are considerably different to those in the coastal cities of China, given the economic disparities that exist. One target for pathology systems in the Asian region is to create a platform where it is possible to share slides and images among colleagues in Asian countries. This has yet to be achieved, although in purely technical terms it would be feasible.

Jun Miyake referred to the comments by Peter Chang, proposing that a very international course be implemented, where the students spend three months each in Japan, China, Korea and Taiwan.

Eun-Cheol Park, Institute for Health Services Research, Yonsei University College of Medicine noted that there were two processes to consider within the context of cancer control and treatment, which are: 1) cure and 2) care. He explained that with regard to the side of cancer care, further attention would be required in Korea, as cancer care is not as well developed as in the United States. Therefore, it would be useful to undertake multidisciplinary studies relating to cancer care, incorporating views from

people other than medical specialists. A trilateral approach would be excellent, although the first steps would not be easy.

Tohru Masui, National Institute of Biomedical Innovation noted that he would like to take the proposal by Jun Miyake seriously, concerning the multiple center one-year study course, noting that it was an ambitious proposal, but one that could provide excellent results. The recruitment of international lecturers would be important as well as students. An e-learning system interlinked among universities would result in the creation of an excellent university course, using such technical aids as video conferencing to overcome cost issues. He invited Taiwan to consider participating too.

Jae Kyung Roh, Yonsei University College of Medicine agreed that this would be a useful way to begin with concrete actions towards the institutionalization of an e-learning-focused, cross-boundary cancer studies program.

Peter Chang, Taipei Medical University noted that students are required to go overseas for six months to one year. He suggested that the program as proposed by Jun Miyake and Tohru Masui could be usefully started from a small scale among interested universities and hospitals, etc.

Yumiko Mochizuki-Kobayashi, Tobacco Policy Research, National Cancer Center proposed incorporating policy research into the cross-boundary studies program. Many disciplines are required to be brought together to conquer cancer and policy research is essential towards this ultimate aim. She noted that the National Cancer Center would be happy to host some training.

Hideyuki Akaza closed the meeting by noting that the Asia Cancer Forum is a very difficult concept in that it

is operating in a diverse region, which makes it difficult to examine specific cancers or treatments, in view of the diversity and disparities in the region. Although efforts have already been made to create trilateral cooperation and cross-boundary cancer studies, unfortunately, however, the number of students enrolling on the course has been small. One solution is to make an exchange program, but to do this would require funding. However, such funding is not available and it will be necessary for Tokyo and Yonsei to cooperate together to see what can be done within the framework of current funding limitations, while seeking other sources from government and the private sector, etc.

He closed the 9th Asia Cancer Forum by emphasizing that it is imperative to continue to work towards the ambitious goal of a multi-country, multidisciplinary program that would involve interaction and cooperation in Asia.

中国で多発する食道癌・胃癌の分子病理学的研究

研究分担者 戸塚 ゆ加里 国立がん研究センター研究所 ユニット長

研究要旨

中国の食道がん・噴門部胃がん多発地域の発がん要因を探索するため、現在、多発地域（磁県）及び低発地域（石家荘）において食道がん・噴門部胃がんの手術検体を収集している。現在までに、それぞれ30症例ずつの生体試料を収集し、これら試料を用いて、DNAアダクトーム解析法により食道がん・噴門部胃がん発生に関与するDNA付加体の探索を行なう予定である。今年度は、生体試料解析の際のDNA付加体標準品データベース構築のため、*in vitro* 反応サンプルの解析をし、各種活性種により生成されるDNA付加体の詳細な評価を行った。活性酸素種や脂質過酸化物質、アルキル化試薬である*N*-nitroso-*N*-methylurea (NMU) と市販のウシ胸腺DNA (ctDNA) を試験管内で反応させ、DNAアダクトーム法を用いて、生成されるDNA付加体を網羅的に解析した。その結果、各種活性種により既知のDNA付加体 (8-oxo-dG, O⁶-Me dG, H⁸dC など) の生成が確認されたのに加え、これまでに報告の無い未知のDNA付加体が多数検出された。それら未知のDNA付加体のうち一つを、詳細な構造解析をした結果、3, N^4 - ϵ 置換型のデオキシシチジンの付加体 CP ϵ dC であることが示唆された。今後は、さらに多様な化学物質と ctDNA の *in vitro* 反応モデルを用いて DNA 付加体標準品のデータベース構築を進めることが、来年度解析する予定の食道がん・噴門部胃がんサンプルの解析に有用であることが期待された。

A. 研究目的

アジア諸国にはがんの高発地域が点在しており、食道がん・噴門部胃がんの好発地域はアジアベルトと呼ばれ、広く知られている。それらの発生起源については、これまでの報告から、アルコール、煙草、漬け物やカビの生えた食べ物の摂取との関係性は薄いことがわかっている。これらのことから、未知の要因によって地域特異的な発がんが生じているものと予測される。アジア地域では毒性の高いカビ毒の一つアフラトキシンによって、

肝臓がんが高頻度で引き起こされていた地域があったことから、食道がん・噴門部胃がんについても地域特徴的な化学物質への曝露が予想される。

そうした曝露があるかどうかは、バイオマーカーの検出の有無や量を解析することで検討される。DNAが反応性を有する化合物と反応した後の修飾体は、DNA付加体と総称される。DNA付加体はバイオマーカーとして発がん要因の検索にしばしば利用される。食道がん・噴門部胃がんについても、発がんを誘発する地域

的な要因があるものと推察されることから、高発地域患者と低発地域患者の非がん部組織の DNA 損傷を解析することで、DNA 損傷の様相に違いがあるかどうかを網羅的に解析する。すなわち、液体クロマトグラフィー連結型質量分析器 (LC-MS) を用い各患者組織中の DNA の損傷の種類や量の違いを比較することで、どういった化合物に曝露されている可能性があるかを予測する。LC-MS を用いて網羅的に DNA 付加体を解析する手法を DNA アダクトーム解析と呼ぶ(図 1)。しかしながら、DNA 付加体のデータベースやすべての付加体を網羅するレビューなどがある訳ではないため、検出された DNA 付加体の同定・アノテーションは独自に行う必要がある。

そこで今年度は、DNA 付加体データのデータベース化を念頭に置いた方針で研究を進めた。

B. 研究方法

データベース構築を進めるための具体的な手法は、以下の 2 つの項目にまとめて示す。

- 1) 既知 DNA 付加体のアダクトームマップ作成
- 2) 食道がん・噴門部胃がんの要因として候補となりそうな化学物質を試験管内で DNA と反応させ、生成される DNA 付加体を LC-MS により網羅的に検出し、既知の付加体ならびに未知の付加体をまとめて一覧化

これらの進捗状況とそれによって得られた成果について報告する。

- 1) 既知 DNA 付加体のアダクトームマップ作成

既知の DNA 付加体のうち、自前に調製が可能な付加体、購入可能な付加体を用意し、LC-MS で分析して保持時間を求めた。(図 2)

- 2) 食道がん・噴門部胃がんの要因として候補となりそうな化学物質の *in vitro* モデル反応

近年、発がん過程において、慢性的な炎症の重要性が指摘されている。そこで、一般に炎症状態で生成されることが知られる活性酸素種 (ROS) と脂質過酸化物質、またアルキル化剤である *N*-nitroso-*N*-methylurea (NMU) と DNA の反応性について、DNA アダクトーム解析を行い検討した。ROS の生成は、硫酸銅と過酸化水素、アスコルビン酸により行った。脂質過酸化物質は、各種脂肪酸(リノール酸、アラキドン酸など)、硫酸銅、アスコルビン酸を混合して行った。上記の混合物あるいは MNU と市販のウシ胸腺 DNA (ctDNA, 終濃度 1.5 mg/mL) を試験管内で 37 °C で反応させ、DNaseI、ヌクレアーゼ P1、アルカリホスファターゼ、ホスホジエステラーゼによりモノデオキシリボヌクレオシドに消化した後、超高速液体クロマトグラフィー連結飛行時間型質量分析器 (UPLC-TOF MS) に供した。化学物質と反応していない ctDNA もコントロールとして用意し、同様に分析した。Waters 社が提供するソフトウェア MarkerLynx を用い、分析データから

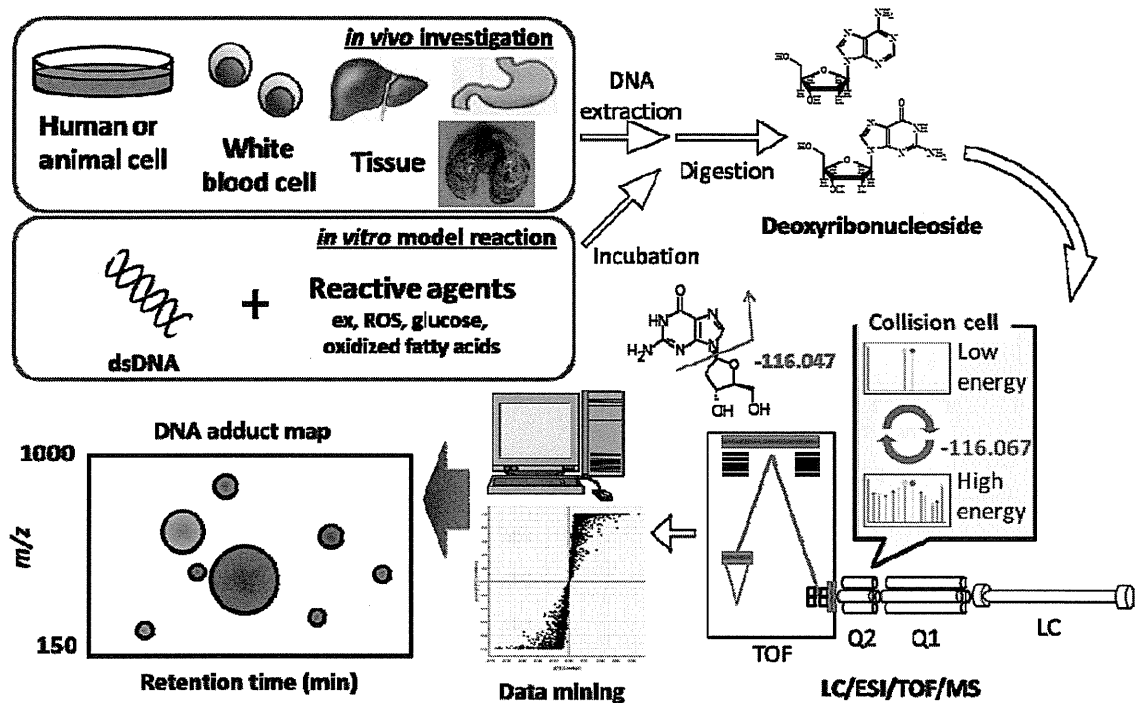


図1. DNAアダクトーム解析の流れ

DNA 付加体の候補となりうるピークを抽出した。また、デオキシリボヌクレオシドに特徴的なニュートラルロス -116.04736 を生じたピークを選択的に抽出することで、ノイズを除去できるように系をデザインした。更に、コントロールである native な ctDNA で検出された DNA 付加体をサンプルの結果から引くことで basal に存在する DNA 付加体を結果から除外した。質量分析の結果得られた各 DNA 付加体の m/z 、保持時間、面積値から DNA 付加体マップを作製した。化学構造が未知の DNA 付加体の構造解析は、MS/MS フラグメンテーション解析と元素組成解析により行った。

(倫理面への配慮)

本研究で行う動物実験にあたっては、国立がん研究センターを含む各施設における動物実験に関する指針に則って実施

し、可能な限り実験動物の苦痛軽減処置を行う。手術標本の残余組織の研究利用については、患者及び家族に対して説明し同意を得る。患者のプライバシーは遵守する。必要に応じて各研究施設の倫理委員会の承諾を得るものとする。疫学研究については、疫学研究に関する倫理指針を遵守する。

C. 研究結果

1) 既知 DNA 付加体のアダクトームマップ作成

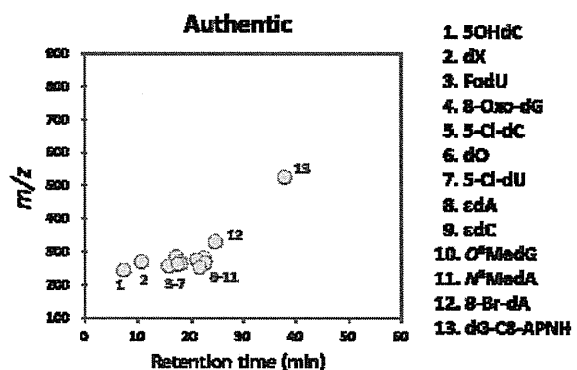


図2. DNA付加体標準品の一覧

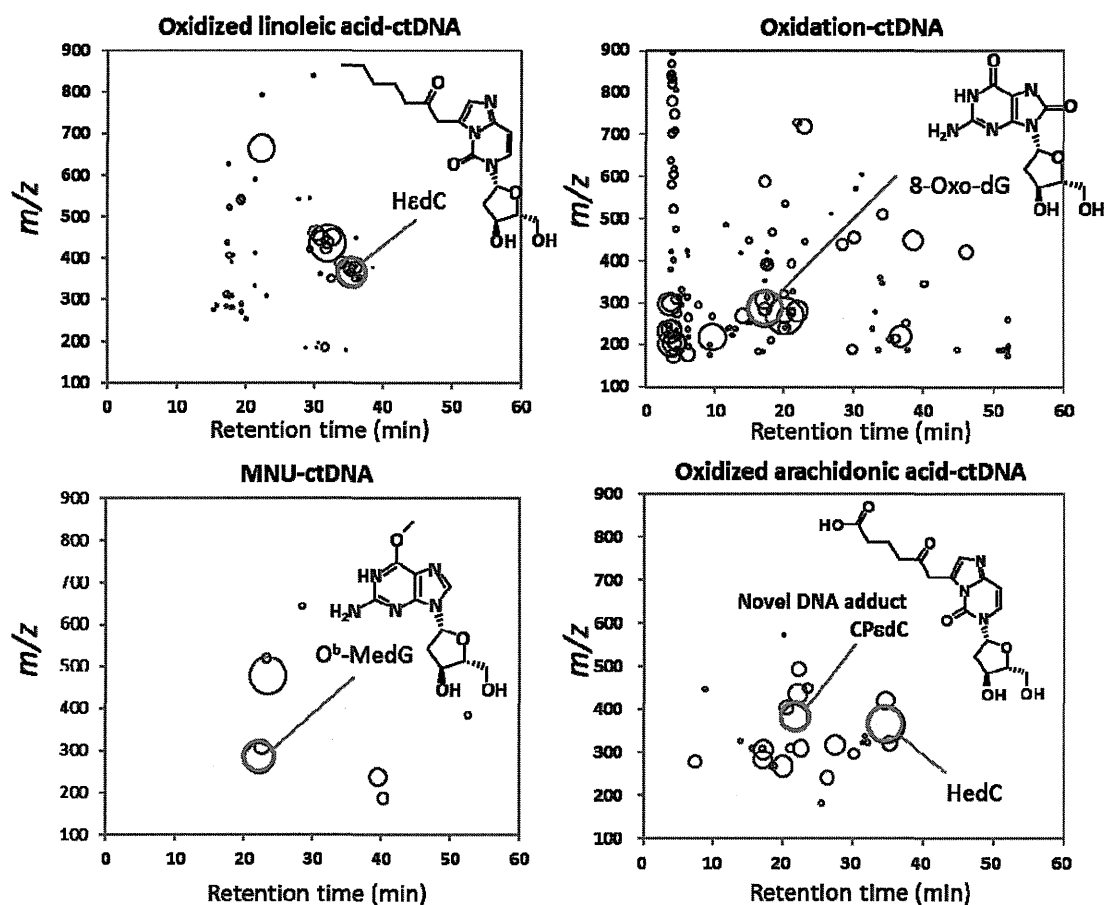


図3. 各試験管内反応のDNAアダクトーム解析結果

図 2 に示すように 1 3 種類の既知 DNA 付加体のマップを作成した。

- 2) 食道がん・噴門部胃がん要因として候補となりそうな化学物質の *in vitro* モデル反応

本年度は、試験管内で行った *in vitro* 反応系において生成される DNA 付加体の解析を行った。その結果、各種反応系において既に報告されている DNA 付加体が検出されたのに加え、未知の DNA 付加体と思われるピークが検出された (図 3)。各反応において生成された DNA 付加体を図中に示した。化学構造が未知の DNA 付加体のうち、生成量が比較的多い付加体の構造解析を行った。その結果、3, *N*-ε 置

換型のデオキシシチジンの付加体 CP_εdC であることがフラグメンテーション解析と元素組成解析の結果から示唆された。

D. 考察

本研究における LC-TOF MS を用いた DNA アダクトーム解析は、小数第二位までの質量を非常に高い精度 (分解能: 約 1 万) で検出できるため、来年度以降、生体試料で行う予定のノンターゲットな網羅的解析を、高い信頼性を保って行うことが出来る利点がある。

本研究の結果、試験管内で行った各種 *in vitro* 反応において、既知の DNA 付加体が複数検出された (図 3)。一方で、そ

れ以上に、これまでに報告の無い化学構造が未知の DNA 付加体が検出された。それらの生成量を見ると、かなり多いものもあることがわかった。これまで、がんのバイオマーカーとして知られる複数の DNA 付加体は *in vitro* 反応から発見されたものが多いことも考慮すると、図 2 で見られたような比較的生成量の多い DNA 付加体の構造解析を行うことは、手術検体を分析するにあたり、必要なプロセスであるものと考えられた。今回、新規 DNA 付加体である CP&C の構造解析が比較的容易に行うことができた知見は、後述するニトロソアミン類により無数に生成される可能性のある DNA 付加体の構造解析などに役立つ情報である。

上述の未知の DNA 付加体の構造解析に加え、試験管内で行った *in vitro* 反応系により生成する DNA 付加体標準品のデータベースの構築についても今後も並行して行う必要がある。しかしながら、自前で調製を行うには多くの労力が必要になるものと予想されるため、来年度は、文献の著者への DNA 付加体標準品の提供の依頼や有機化学者に共同研究を呼びかけることも視野に入れたい。

食道がん・噴門部胃がんの高発地域における発がん要因の解析は古くからおこなわれている。様々な要因と相関が無いことがわかっているが、高発地域の井戸水に硝酸塩が多く含まれているとの報告があり、それらを摂取した際に胃内で産生される可能性のあるニトロソアミン類への曝露が発がん要因として注目されている。ニトロソアミン類は強い変異原性を有しており、動物発がん実験では頻繁

に利用されている。今回用いた MNU はニトロソアミン類の一種であり、MNU-ctDNA の反応で検出された O⁶-MedG は複数のニトロソアミン類から共通して生成されることがわかっていることから、ニトロソアミン類への曝露を評価するバイオマーカーになりうる可能性が期待され、食道がん・噴門部胃がんサンプルでルーチンに分析することで、ニトロソアミン類への曝露を明らかにできるかも知れない。その一方で、ニトロソアミン類は、食品中に存在する二級アミンを有する化合物の数だけ種類が存在する可能性があるため、曝露されうるニトロソアミンの種類は未だ明らかになっていない。そのため DNA アダクトーム解析法のような網羅的な解析手法により、新たなバイオマーカー候補が見つかる可能性も期待できる。

現在、中国河北省の磁県（高発地域）と石家庄（低発地域）において生体試料を収集している。既に高発および低発地域それぞれから 30 症例分の手術検体および末梢血の収集に成功した。来年度は、これら試料から DNA を抽出し、DNA アダクトーム解析法を用いて、食道がん・噴門部胃がん発生に關与する DNA 付加体の探索を行う予定である。

E. 結論

本研究では、試験管内で行った DNA と活性種の *in vitro* 反応サンプルを、DNA アダクトーム法を用いて解析した。種々の活性種と ctDNA を反応後、モノデオキシリボヌクレオシドに酵素消化し、LC-MS で分析したところ、既知の DNA

付加体に加え、未知の DNA 付加体が複数検出された。未知の DNA 付加体のうち、MS/MS フラグメンテーション解析と元素組成解析を行うことで、CP&dC の化学構造解析を行った。次年度は、収集した食道がん・噴門部胃がんの手術検体を精力的に分析し、好発地域の患者の DNA に見られる DNA 付加体を解析する。

F. 健康危険情報

(総括研究報告書にまとめて記入)

特に無し

G. 研究発表

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H. 知的財産権の出願・登録状況 (予定を含む)

1. 特許取得
特になし

2. 実用新案登録
特になし

3. その他
特になし

アジア諸国におけるがん流行の動向分析

研究分担者 片野田耕太

国立がん研究センターがん対策情報センターがん統計研究部がん統計解析室長

研究要旨

がんの最大の危険因子である喫煙について、日本、中国、および韓国における状況の分析を行った。中国および韓国の資料については、現地の研究協力者の支援を得て資料を収集し、収集した資料が不十分な分野については、中国および韓国での産業・市場調査を専門とする調査会社に調査を依頼した。日本側の資料については、政府統計などを中心に、可能な限り比較可能な資料を収集した。成人（20～60歳代）の現在喫煙率は、男性では中国が、女性では日本が最も高かった（日本男性 36.7%、女性 10.4%、中国男性 52.9%、女性 2.4%、韓国男性 48.3%、女性 6.3%（いずれも 2009 年））。成人の受動喫煙は家庭、職場とも中国では曝露割合が 50%を超え、日本でも職場では男性で 45.9%、家庭では女性で 27.5%、韓国では職場で男女とも 40%を超えていた。禁煙試行率は日本が最も低く、禁煙補助の利用割合は三か国とも低かった。将来的に中国がたばこ市場を開放することが予想されており、東アジアが連携して、たばこ価格の値上げ、禁煙治療薬の普及、および屋内空間の禁煙法制化を進める必要がある。

研究協力者

Jiang Yuan

National Tobacco Control Office,
Chinese Center for Disease Control and
Prevention, China

Sohee Park

Department of Epidemiology and
Health Promotion, Graduate School of
Public Health, Yonsei University, Seoul,
Korea

Min Kyung Lim

National Cancer Information Center,
National Cancer Control Institute,
National Cancer Center, Korea

A. 研究目的

東アジアは世界でも喫煙率が高い地域であり、男性の喫煙率（紙巻たばこ、以下同じ）が女性より顕著に高いことを大きな特徴としている。Tobacco Atlas における男性喫煙率は、中国 52.9%、韓国 47.7%、日本 38.2%であり、中国と日本はたばこ消費がそれぞれ第 1 位と第 5 位である[1]。これらの三か国は、喫煙習慣の普及状況などで共通する背景を持つと考えられるが、たばこ対策における情報共有や共同研究は包括的には行われていない。本研究は、たばこ対策における東ア

ジアの現状について、日本、中国、および韓国の現状分析を行った。

B. 研究方法

日中韓三か国に関して、先行研究[2]で収集した情報のうち更新可能な以下の項目の更新を行った。

能動喫煙曝露状況

受動喫煙曝露状況

喫煙者の禁煙行動

中国および韓国については研究協力者に資料収集を依頼した。収集した資料が不十分な分野については、中国および韓国での産業・市場調査を専門とする調査会社に調査を依頼した。

日本側の資料については、政府統計などを中心に、上記分野の資料を収集した。

(倫理面への配慮) 本研究では公表されたデータのみを使用しているため、倫理的な問題は生じない。

C. 研究結果

日本、中国、韓国の三か国について、2010年の比較可能なデータの収集が可能であった。図1～図4に結果を示す。三か国の比較により、以下の特徴が明らかになった。

- ・日本では35%前後、中国および韓国では50%前後の男性が喫煙者であり、三か国とも30～40歳代で最も高い(中国と韓国では約60%)。
- ・日本では男女とも喫煙者の禁煙試行率が中国および韓国より低い。
- ・三か国とも、禁煙試行者における禁煙補助の利用割合が低い。

- ・三か国とも、男性の40%以上が職場で受動喫煙に曝されており、中国では曝露割合は70%前後である。

- ・中国では女性の60%以上が家庭で受動喫煙に曝されており、日本でも曝露割合は約30%である。

D. 考察

日本、中国、および韓国の東アジア三か国では、男性の喫煙率がいまだ高く、受動喫煙の曝露割合が高い。喫煙者の禁煙試行率が低く、禁煙試行者の大多数は禁煙補助薬などを利用せずに禁煙試行をしている。これらの状況から、東アジアにおけるたばこ対策の優先的な政策は、

- ・成人男性の禁煙試行率を上げるための値上げとメディアキャンペーン
- ・科学的根拠に基づく禁煙補助の制度的拡充
- ・公共の場所での禁煙の法制化(特に職場)

の3つであると考えられる。わが国では2010年にたばこ価格が1箱平均100円近く値上げされ、2010年の成人男性喫煙率は前年から6ポイント減少したが、2011年には逆に増加した(38.2%→32.2%→32.4%) [3]。韓国では、たばこ税の値上げによる増収をたばこ対策の目的に用いる制度が始められた。また、韓国では、全国の保健センターで禁煙治療薬が無料利用できる制度が始まっている。

受動喫煙防止の法制化については、三か国とも公共の場所での法規制が地域レベルで進んでいるが、職場については規制が遅れている。わが国では2010年以降、労働安全衛生法改正が受動喫煙防止措置

を事業者の義務とする方向で進められたが、2012年の衆議院解散によって廃案となった。台湾では、2009年にほぼすべての職場と公共の場所の禁煙が法制化され、たばこ製品のラベルに写真付きの警告表示を掲載した。

中国は2001年に世界貿易機関(WTO)に参加した。日本たばこ産業を始めとして、国際的なたばこ産業は中国市場の開放を視野に入れて、中国たばこ産業との連携を画策している[4]。たばこ産業の国際的な動きに対抗するためには、東アジア各国が互いの先進事例を学び、連携してたばこ対策を推進する必要がある。

E. 結論

たばこ対策について日本、中国、および韓国の現状を比較した結果、男性喫煙率が高い、禁煙治療の普及が進んでいない、受動喫煙曝露割合が高いなど、共通の特徴が明らかになった。

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F. 健康危険情報

なし

G. 研究発表

論文発表

(なし)

H. 知的財産権の出願・登録状況

(なし)