The Chinese Epidemiological Approach of Nasopharyngeal Carcinoma Research and Control

G. DE-THÉ

CNRS, Faculty of Medicine A. Carrel, Lyon, and IRSC, Villejuif, France

Received October 8, 1980

Nasopharyngeal carcinoma (NPC), the major cancer killer in Cantonese Chinese, represents one of the three cancer research priorities in China. Apart from some fundamental research projects on the Epstein-Barr virus (EBV), their main efforts are epidemiologically and clinically oriented. Major surveys in GuangDong and GuangXi provinces showed that high EBV/IgA/VCA serum levels can detect NPC at an early stage of the disease. Characterization of "precancerous lesions" in the nasopharynx and among the EBV/IgA positive individuals is in progress in the Zangwu county of the GuangXi Autonomous Region. Preventive anti-viral intervention in these individuals is being discussed. Search for genetic and environmental chemical carcinogens is also carried out. This Chinese epidemiological approach complements well the fundamental Western studies on EBV and NPC.

INTRODUCTION

As a major national effort, a comprehensive cancer survey was undertaken in the People's Republic of China, between 1974 and 1976. It covered the 29 provinces, 2,392 counties and involved a population of 850 million individuals. The results are being published in an atlas of Cancer Mortality in China by Dr. Li Ping, Head of the National Cancer Control Office of the Ministry of Health and Director of the Cancer Research Institute of the Chinese Academy of Medical Sciences, Peking [1]. The order of frequency for the country and the geographical preponderance of the 700,000 tumors detected annually in the People's Republic of China is shown in Table 1.

Three cancer sites show a specific geographical distribution and were declared research priorities at the national level: cancer of the esophagus in the north central area, under the responsibility of the Cancer Institute of the Academy of Medical Sciences in Peking; primary liver carcinoma in the southeastern area, under the coordination of the Shanghai Cancer Institute; and nasopharyngeal carcinoma in the south, under the chairmanship of the Guangzhou Cancer Institute.

Setting medical research priorities is a must in developing countries, but in China there is much more to it. The Chinese priorities are mainly geared toward primary and secondary prevention; i.e., toward the characterization of risk factors (that will have to be eliminated) and early detection through major mass surveys. While Western nations have a "curative" health system and an analytical research mind, Chinese tend to consider prevention as the only valuable health approach and a

Parts of this paper were presented at the medical symposium sponsored by the Yale-China Association on September 13, 1979. Convener: G.D. Hsiung

Address reprint requests to: G. de-Thé, CNRS, Faculty of Medicine A. Carrel, Rue Guillaume Paradin, F. 69372 Lyon CEDEX 2, France

Copyright © 1981 by The Yale Journal of Biology and Medicine, Inc.
All rights of reproduction in any form reserved.
pragmatic way to control diseases without necessarily knowing their precise etiology or pathogenesis.

This approach, which goes back thousands of years, is leading at the present time to multifactorial intervention in high-risk communities in a most pragmatic manner, even before having well delimited the risk factors. In 1949, top priority was given to health problems. In the cancer field, the results of Doll[2], indicating the critical role of the environment and life style in the development of most carcinomas, were taken as the basis of a cancer research program. The Chinese decided that the best way was to define risk factors and to set up preventive interventions. China thus offers the possibility of conducting epidemiological studies unthinkable in the Western world. Post-Mao China is changing rapidly, and fundamental research has been quickly reinstalled in most cancer centers. This may promote a well-balanced, integrated, fundamental and applied research program.

The content of the present paper refers to information gathered during a visit to the main Chinese cancer centers in July 1979 and during a collaborative field study trip in Zangwu County of the GuangXi Autonomous Region with Dr. Zeng and collaborators in April–May 1980.

EPIDEMIOLOGY OF NASOPHARYNGEAL CARCINOMA (NPC) IN CHINA

Figure 1 shows the dramatic geographical restriction of the NPC distribution in South China [1]. In GuangDong province, which represents more than 50 million individuals, NPC is the most common type of cancer. It represents 43 percent of all cancers in males and 16 percent in females [3]. The minimal age-adjusted prevalence rate for NPC during the period 1970–1972 was found to be 40/100,000 and 23/100,000 for males and females, respectively [4].

Of particular interest was the geographical variation observed in GuangDong province. The central and southern parts of GuangDong province exhibit the highest rate for NPC and correspond relatively well to the Pearl River Basin inhabited by Cantonese, the main ethnic group in size, with an incidence rate of NPC of 10 to 20/100,000 per year.

The Tanka or boat-dwellers of the Pearl River are at an even higher risk for this cancer (incidence = 55/100,000 per year); the Chao-Chow, living in the northeast part of the province, and the Hakka, northern migrants, both have an intermediate risk for NPC (incidence = 5 to 10/100,000 per year) [Li Chen Chuan, personal communication]. Such geographical variations most probably reflect dietary and cultural customs.

In the adjacent GuangXi Autonomous Region, NPC is prevalent mostly in the
FIG. 1. Geographic variations of the mortality rates for nasopharyngeal carcinoma (NPC) in the People's Republic of China. The dark areas refer to the highest prevalence, where NPC represents up to 43 percent of all cancers in males. In these areas, centered on GuangDong province and extending along the South China Sea's shores in Fujian province, the crude annual mortality rates range from 11 to 25 per 100,000 inhabitants. The shaded areas refer to intermediate prevalence of NPC, with annual mortality rates varying from 2 to 10 per 100,000 inhabitants. These cover part of the GuangXi Autonomous Region and the provinces of Hunan, JiangXi, and Fujian. (Source: Dr. Li Ping: Atlas of cancer mortality in the People's Republic of China. Edited by the Cancer Institute, Chinese Academy of Medical Sciences. Beijing, in press)

eastern part inhabited by the Han, which includes the Zangwu County where an NPC field station has been set up.

Along the western Pearl River, the NPC incidence is comparable to that of Guangzhou. In the province of Hunan, adjoining GuangDong to the north, NPC has a relatively low incidence, except in the Miao western area, where NPC is high.

Such a geographical distribution suggests a strong environmental or rather cultural factor, possibly linked to nutrition, such as nitrosamine-contaminated fishes.
SEARCH FOR CHEMICAL CARCINOGENS

Whereas this field of research has been very active in relation to the cancer of the esophagus in the central part of China with the evidence of nitrosamines and nitrates in pickled vegetables, only minor efforts have been devoted to similar studies with regard to nasopharyngeal carcinoma.

Ho [5-6] has repeatedly claimed that the cultural habits of the Cantonese Chinese in eating salted fish is linked to the risk of developing nasopharyngeal carcinoma. Huang et al. [7-8] found nitrosamines in such salted fish and succeeded in inducing tumors of the nasal fossae in rats fed with salted fish. The belief of Ho in such a cultural factor is so strong that a few years ago he launched a vigorous public campaign to prevent mothers from giving such delicate food to weaning babies. Chinese epidemiologists in Shanghai, Changsha, or Kwangchow do not believe that this habit could represent an important risk factor, as the areas where this habit is very common do not correspond systematically to the areas with high NPC incidence. However, Dr. Pan Chih-Cheng of the Human Medical College in Changsha has, together with Dr. Yas Kai Pai, carried out studies on nitrosamines in rats, in line with Ho's results.

By inoculating 50 mg-kg weight of nitroso-piperazine compound subcutaneously in rats, she obtained tumors of the nasal fossae, of the esophagus, and of the liver [personal communication]. Unfortunately, no epidemiological study has been carried out, to our knowledge, in China, comparing the salted fish eating habit in populations with high and low risk for NPC. Zangwu County of the GuangXi Autonomous Region, with neighboring populations exhibiting high and low risks for nasopharyngeal carcinoma, would be suitable for such studies.

VIROLOGICAL STUDIES

Whereas in the Occidental World most studies on the Epstein-Barr virus (EBV) are related to fundamental research [9-12], the Chinese priorities are geared to a better control of nasopharyngeal carcinoma using the association with EBV. This led to epidemiologically oriented and clinical research projects on early diagnosis, with laboratory support. Cancer research institutes and basic virus laboratories are progressively implementing new basic virological (cell biology and molecular) projects on EBV, mostly in Peking (Institute of Virology and Cancer Institute), in Shanghai (Institute of Cell Biology), and in Guangzhou (Cancer Institute) but also in universities, such as the Hunan Medical College in Changsha. Pertinent to this point is the world's first success in obtaining an established epithelial NPC-derived cell line [13]. Population-oriented studies on NPC have focused first on patients evaluating the strength of the EBV association by serology, IgG antibodies to Virion Capsid Antigens (VCA), Early Antigens (EA), and Epstein-Barr Nuclear Antigens (EBNA), and then on mass population surveys to assess the usefulness of EBV serology to detect NPC at a very early stage of the disease, when treatment is less expensive and more efficient. For such a purpose they developed immunoenzymatic tests for detecting antibodies to VCA, EA, and EBNA in field conditions [15-16].

Population surveys involved two steps: first, serological surveys aimed at detecting individuals with high IgA antibodies to VCA, then clinical surveys aimed at characterizing pre-NPC lesions of the nasopharynx [14]. Two major studies were carried out in that direction in South China. Around Guangzhou, Dr. Li Chen Chuan of the GuangDong Cancer Hospital and Cancer Institute (Director, Dr. Tseung) organized a massive clinical survey involving more than 32,000 normal individuals. On carefully examining 494 nasopharyngeal mucosae, they found 48
nodular alterations of the mucosa, 28 hyperplastic adenoids, 9 follicular hyperplasias, 4 cases with numerous petechia, and 5 atrophic mucosae, two of them being found to be NPC [Dr. Li and Dr. Tseung, personal communication].

In the eastern part of the GuangXi Autonomous Region, Dr. Zeng of the Virus Institute in Peking, in collaboration with the GuangXi Department of Public Health, surveyed in the Zangwu county a total of 148,000 normal individuals aged 30 years and above. By the immunoenzymatic test they developed [15] and in two successive studies, Zeng et al. found around 1,300 individuals with IgA/VCA titers 1:25 or higher [17]. Clinical investigations of these individuals led to the finding of 46 NPC cases, about one-half at early stages (I and II) of the disease [16; Zeng et al., personal communication]. Careful follow-up of these IgA-positive individuals showed that one and a half years after the original clinical survey, 12 more developed NPC, indicating a minimal incidence of 250 per 100,000 among the IgA-positive individuals, more than twenty times higher than that of the general population of the same area (20/100,000) [Zeng et al., personal communication]. Clinical examination of 1,150 of these IgA-positive individuals showed 335 macroscopic abnormalities of the nasopharyngeal mucosa. Out of 203 biopsies taken on the most obvious abnormalities, histopathological examination showed 78 inflammatory processes, 66 lymphoid hyperplasia, 46 NPC (see above), and 13 normal mucosa [NPC collaborating group in Zangwu chaired by Dr. Zeng, personal communication].

In order to better characterize the macroscopic, microscopic, and virological lesions of the nasopharynx preceeding the development of NPC, we carried out in April–May 1980, with Dr. Zeng and his collaborators, a detailed investigation of 56 individuals in the Zangwu county Cancer Center selected for their high IgA titers. Four NPC cases were again discovered and seven inflammatory lesions showed some EBNA positive cells by ACIF test on smears [18; Desgranges et al., in preparation]. A search for EBV DNA in the collected biopsies in being carried out in collaboration with Dr. Bornkamm from Dr. Zur Hausen's laboratory in Freiburg, Federal Republic of Germany. Careful follow-up of these 56 individuals will tell whether lesions of the nasopharynx with EBV markers do represent pre-cancerous lesions or not.

In another field study, Zeng et al. [personal communication] are collecting exfoliated cells from the nasopharyngeal mucosa of NPC and non-NPC individuals, by negative pressure suction. These mostly epithelial exfoliated cells are being tested for the presence of EBNA by their immunoenzymatic method [16]. Preliminary results indicate that EBNA is detectable not only in NPC tumor cells, but also in hypertrophic and normal-looking epithelial cells [19].

GENETIC STUDIES

Cytogenetic studies have been carried out on NPC-derived lymphoblastoid lines in Peking Cancer Institute, in Shanghai, Changsha, and in Guangzhou. Giant group A marker chromosomes have been detected by Chinese investigators in various proportions of such cell lines [20]. Short-term epithelial outgrowths from NPC have also shown such cytogenetic abnormalities. Ou et al. in Guangzhou Cancer Institute reported the presence of giant sub meta centric chromosomes in 18 epithelial explants of 48 NPC biopsies put in culture [personal communication]. The major drawback is the difficulty of obtaining dividing epithelial cells in vitro.

Multiple NPC case families have been searched for at the Guangzhou Cancer Institute. Ou et al. [personal communication] found that 5 to 6 percent of the NPC cases seen at the Cancer Hospital are occurring in families where two or more cases of
NPC have been observed. Unfortunately, the limit of the family is not given. Dr. Tang in Shanghai ENT Hospital is also looking at the same problem and has observed a number of families with multiple cases [personal communication]. It is worth noting at this point that there is a taboo about first-cousin marriage on the paternal side in China, but that this is not the case for cousins from the maternal side. Ho has repeatedly reported families with multiple cases of NPC [5-6]. HLA (Human Leukocyte Antigens) studies in relation to NPC have not yet been fully implemented in China. One would like to see if the results of Simons et al. [21] who showed that the haplotype A2BW46 in Chinese carries an increased risk of 2 vis-à-vis the general population can be extended to China. Dr. Simons is helping to set up an HLA typing laboratory in the Cancer Institute in Guangzhou. The determination of different genetic traits including HLA-DR in multiple NPC case families should bring significant new data on this important question.

PREVENTIVE INTERVENTIONS

As discussed in the introduction to this paper, the main aim of the Cancer Control Program in China is to implement multifactorial interventions with the hope of somewhere breaking the chain of events before the clinical development of the tumor. In the high esophagus cancer areas, populations are discouraged from eating pickled vegetables and are advised to add vitamin C to their food, thus decreasing the nitrate level in their urine. No report to our knowledge is available to assess the value of this intervention.

In the field of nasopharyngeal carcinoma, little effort is made to try and discourage people from eating salted fish in China, in contrast to the effort of Dr. Ho in Hongkong, who launched a major information campaign to convince parents to stop giving salted fish to weaned babies. The field studies carried out in the Zangwu county and the finding of high-risk individuals characterized by high serum IgA/VCA titers represent a unique opportunity to consider the possibility of a selected prevention against NPC through antiviral intervention.

The basic hypothesis is that the clinical development of NPC is accompanied by or better is preceded by a reactivation of the latent infection by EBV in the nasopharyngeal mucosa. Such a reactivation is reflected by the presence of IgA in the serum and in the nasopharyngeal mucosa. If one could successfully treat such EBV reactivation in the nasopharynx, reverse the organism's trend of increasing the serum IgA/VCA titers, and see if such intervention prevents the development of NPC, the causal involvement of EBV would be established and a new approach for NPC prevention achieved. Anti-viral intervention could be carried out either by treatment by interferon or by chemotherapy involving compounds such as acycloguanosine.

An active immunotherapy using cell surface-determined EBV antigens is also a possibility to be investigated. The feasibility of such interventions remains to be evaluated from the experimental as well as the epidemiological and ethical viewpoints. But the Chinese approach to cancer research allows such possibilities, and we are confident that they will succeed in bringing further important epidemiological studies, in achieving systematic early detection, and we hope in preventing NPC in a reasonable period of time.

REFERENCES

1. Cancer Institute (Hospital) Chinese Academy of Medical Sciences: Annual report 1978 and Atlas of Cancer Mortality in China. Beijing, Department of Virology of the Cancer Institute, in press
2. Doll R: Epidemiology of Cancer: Current Perspectives. Am J Epid 104:396-405, 1976
3. Kaplan H, Tsuchitani PJ: Cancer in China. New York, Alan R. Liss, 1978, pp 83–100
4. Henderson BE: Observations on Cancer Etiology in China. In Second symposium on Epidemiology and Cancer Registries in the Pacific Basin. J Nat Cancer Inst monograph number 53, 1979, pp 59-65
5. Ho JHC: Nasopharyngeal Carcinoma in Hongkong. In Cancer of the nasopharynx. (Edited by CS Muir, K Shanmugaratnam. UICC monograph series, Vol 1. Copenhagen, Munksgaard, 1967, pp 58–63
6. Ho JHC: Current knowledge of the epidemiology of nasopharyngeal carcinoma—a review. In Oncogenesis and Herpesviruses. Edited by PM Biggs, G. de-Thé, LN Payne. IARC scientific publication number 2. Lyon, 1972, pp 357-366
7. Huang et al: Analysis for volatile nitrosamines in salt-preserved foodstuffs traditionally consumed by southern Chinese. In Nasopharyngeal Carcinoma: Etiology and Control. Edited by G de-Thé, Y Ito. IARC Scientific publication number 20. Lyon, 1978, pp 309–314
8. Huang et al: Carcinoma of the nasal and paranasal regions in rats fed Cantonese salted marine fish. In Nasopharyngeal Carcinoma: Etiology and Control. Edited by G de-Thé, Y Ito. IARC Scientific Publication number 20. Lyon, 1978, pp 316–328
9. Adams A: Molecular Biology of the Epstein-Barr virus. In Viral Oncology. Edited by G Klein. New York, Raven Press, 1980, pp 683–712
10. Miller G: Biology of the Epstein-Barr virus. In Viral Oncology. Edited by G Klein. New York, Raven Press, 1980, pp 713–738
11. Pearson G: Epstein-Barr virus: immunology. In Viral Oncology. Edited by G Klein. New York, Raven Press, 1980, pp 739–768
12. De-Thé G: Role of the Epstein-Barr virus in Human Diseases: Infectious Mononucleosis, Burkitt's Lymphoma and Nasopharyngeal Carcinoma. In Viral Oncology. Edited by G Klein. New York, Raven Press, 1980, pp 769–797
13. Cancer Institute and Institute of Virology, Beijing: Establishment of an epithelioid cell line and a fusiform cell line from a patient with nasopharyngeal carcinoma. Scientia Sinica: 1–27, 1978
14. Zeng Y, Shang M, Liu CR, et al: Detection of anti-Epstein-Barr virus IgA in NPC patients in 8 provinces and cities in China. Chinese Oncology: 1–2, 1979
15. Lin YX, Zeng Y: Detection of Epstein-Barr virus specific IgA antibody from patients with nasopharyngeal carcinoma by immunoenzymatic method. Chinese J Oncology 1:8, 1979
16. Zeng Y, Pi GH, Zhao WP: Detection of EBNA by anticomplement immunoenzymatic method. Acta Acad Med Sin 2:134–135, 1980
17. Zeng Y, Liu YX, Liu CR, et al: Application of an Immunoenzymatic Method and an Immunoautoradiographic Method for a Mass Survey of Nasopharyngeal Carcinoma. Intervirology 13:162–168, 1980
18. De-Thé G, Desgranges C, Zeng Y, et al: Search for pre-cancerous lesions and EBV markers in the nasopharynx of IgA positive individuals. XII. International Symposium on nasopharyngeal carcinoma, Düsseldorf, Fed Rep of Germany, October 23–25, 1980
19. Zeng Y, Shen S, Pi G, et al: Application of anticomplement immunoenzymatic method for the detection of EBNA in carcinoma cells and normal epithelial cells from the nasopharynx. XII. International Symposium on nasopharyngeal carcinoma. Düsseldorf, Fed Rep of Germany, October 23–25, 1980
20. Wu P, Wu YQ, Li YW, et al: Studies of Giant Group A marker chromosome in several Burkitt's lymphomas and lymphoblastoid cell lines with Epstein-Barr virus from different origins. Chinese J Oncology 1:2, 1979
21. Simons MJ, et al: Nasopharyngeal Carcinoma and Histocompatibility Antigens. In Nasopharyngeal Carcinoma, Etiology and Control. Edited by G de-Thé, Y Ito. IARC Scientific Publication number 20. Lyon, 1978, pp 271–282