The “Sufficiency Principle” from the Perspective of Cancer Prevention

To the Editor:

The 27th International Symposium of the Princess Takamatsu Cancer Research Fund brought together scientists from several countries to present their work related to the title “Fundamentals of Cancer Prevention”. The recently published proceedings from that symposium (1) included introductory remarks in which Dr. T. Sugimura discussed the “Sufficiency Principle”, citing Rothman’s paper (2), for the multi-factorial nature of gastric cancer (3). Figure 1A in that paper shows how various carcinogenic factors cause sufficient genetic damage to convert normal cells into cancer cells, Fig.1B indicates the reduction of carcinogenic risk factors, and Fig.1C represents the summation of reductions, leading to “insufficiency” of genetic alterations (3-5).

Because of the subject matter of the proceedings, it struck me that the Sufficiency Principle might be viewed from the opposite direction, i.e. from the perspective of the preventive agent rather than the carcinogenic risk factors. Thus, in reference (3), Fig. 1A might define the “Sufficiency of Protection” required to give complete coverage, via a combination of preventive measures acting by multiple mechanisms and covering all stages of carcinogenesis (a-h). The preventive measures would include exposure to “blocking agents” during the initiation phase and “suppressing agents” for the post-initiation and progression phases of carcinogenesis, as defined by Wattenberg (6). Avoidance strategies also would be included, based on the “Twelve Points for Cancer Prevention” (7,8), such as cessation of cigarette smoking and reducing the intake of charred foods and excess calories (9-11). If Fig.1A in reference (3) defines the Sufficiency of Protection, Fig.1B represents the “Insufficiency of Preventive Measures”. The net result of this lowered protection would be to allow multiple genetic changes to occur by exposure to endogenous and external factors (white areas in Fig.1B). As a consequence, mutations accumulate in various genes (a’,c’, d’,e’,f’,h’ in Fig.1C), and convert a normal cell to a cancer cell.

One might further choose to illustrate these ideas in the context of colorectal carcinogenesis, with reference to the findings reported in the proceedings (1). To provide the coverage required by the Sufficiency Principle for the multifactorial nature of colon cancer inhibition (Fig.1A), an individual would be exposed to a combination of preventive agents and measures, including the following (though not necessarily in order of priority): (a) arachadonic acid cascade inhibitors, (b) polyphenols, (c) flavonoids, (d) organosulfur compounds, (e) trace elements, (f) conjugated linoleic and docosahexaenoic acids, (g) xanthophylls, chlorophylls, and carotenoids, and (h) low fat and caloric intake, and dietary restriction (1). An insufficiency of (a)-(h) would allow multiple genetic hits to occur in key genes (Fig.1B, white areas). In the example of colorectal cancer, the key genes might include several of the following: (a’) APC, (c’) CTNNBI, (d’) Ki-ras, (e’) DCC, (f’) P53, and (h’) BAX (Fig.1C) (12-15).

As defined here, the Insufficiency Principle represents one of the “Fundamentals of Cancer Prevention”, since it describes the loss of protective agents and measures to such an extent that genetic alterations accumulate and normal cells develop into cancer cells.

References

10. Sugimura T. Past, present, and future of mutagens in cooked foods. Environ Health Persp 1986;67:5-10

Abbreviations: APC, adenomatous polyposis coli gene; CTNNBI, β-catenin gene

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The Pre-conceived British Beliefs of Gastric Cancer in Japan Need to be Changed

To the Editor:
British surgeons have long been criticised for their poor quality research and reliance on historical reviews of their own personal series. A brief read of any surgical journal over the last five years will seldom reveal a randomised surgical trial, a point noted by Richard Horton (Editor of The Lancet) when he described British surgical research as comic opera (1).

When British surgeons compare their own results for gastric cancer surgery with those of Japanese surgeons, two excuses are offered: firstly gastric cancer in Japan is a different disease than in the West and secondly Japanese surgeons refuse to test their hypotheses in randomised clinical trials. I have recently had the opportunity to visit the National Cancer Center Hospital (NCCH) in Tokyo and feel that after such a thorough introduction to Japanese gastric surgical practice I can address these two misconceptions.

The gastric surgery division of the NCCH, in conjunction with the endoscopy division, will treat approximately 430 gastric cancer cases per year. Approximately 60% of these will be early gastric cancer (limited to the mucosa and submucosa only) whereas the proportion of early cases in the UK is nearer to 20% (2). The incidence of gastric cancer in Japan, however, is approximately five times that in the UK. The Japanese government established a screening programme 30 years ago and this, in conjunction with greater population awareness has led to the greater proportion of early disease being treated. In 1996, 40% of gastric cancer patients treated by the gastric surgery division underwent either total or proximal gastrectomy, while in the recent MRC randomised controlled trial, 56% of patients underwent a total gastrectomy (2). The incidence of proximal tumours is certainly increasing in the UK but the differences between the UK and Japan are only slight. In my two-month stay at the NCCH, I reviewed the radiology and witnessed the treatment of all stages of gastric cancer. There is no doubt in my mind that, apart from the proportion of early stage disease, gastric cancer in Japan appears both macroscopically and microscopically to be exactly the same as gastric cancer in the UK.

The standard gastrectomy in Japan is a D2 resection and this is performed with almost no mortality and minimal morbidity. It is true that Japanese surgeons are not prepared to test their standard resection against the British D1 resection. The surgical mortality rates at the NCCH are under 1%, when this is compared to the 6.5% mortality rate in the D1 resection group in the MRC trial and the fact that the NCCH can achieve an overall five-year survival rate of 71.8% (all stages), who can blame them (2,3).

Japanese surgeons, like surgeons all over the world, are constantly looking at methods of improving their survival rates and so the D4 resection was devised. A D4 dissection can now be performed with no increased mortality over a D2 dissection, with only a slightly longer post-operative stay and a slightly higher morbidity. The safety and tolerability of the treatment has therefore, been established. It is at this point that the British surgical community would expect their Japanese colleagues to amass a large personal series and present and publish their data recommending this procedure as the cure for gastric cancer. This approach may have been true in the past but it is no longer the case.

The Japanese Clinical Oncology Group (JCOG) consists of major oncology centres (both public and private) around Japan who co-operate in clinical trials (4). Study number JCOG 9501 is one of five current studies in gastric cancer, four of which are run by JCOG. This study is designed to compare the standard D2 dissection with a D4 dissection in patients with advanced gastric cancer. The hypothesis is that patients with a locally advanced tumour, i.e. at least involvement of the subserosal layer but without evidence of distant or peritoneal disease, will benefit from an extended lymphadenectomy. The eligibility criteria are strict, to ensure that only the correct sub-groups are included and the patients are randomised during the operation. Recruitment started 18 months ago and 155 patients have been recruited to date with a total of 404 needed to complete the study.

Study number JCOG 9502 is a randomised trial in patients with tumours of the cardia encroaching on the oesophagus. Patients are randomised to either an abdominal approach or to a thoraco-abdominal approach, which may allow a more radical lymphadenectomy at the expense of a higher operative mortality. Two randomised studies of adjuvant chemotherapy are currently recruiting; one in patients with positive peritoneal cytology (JCOG 9701) and a second in patients with pT2 disease and lymph node metastases (NASAS-GC). A randomised study of adjuvant chemotherapy in tumours without serosal involvement (JCOG 9206–1) has recently finished recruiting and a study of adjuvant chemotherapy in locally advanced tumours (JCOG 9206–2) is due to complete recruitment in March 1998. It appears that Japanese surgeons are willing to test their hypotheses in randomised clinical trials and that Japanese patients will consent to such trials when appropriately counselled. Perhaps of more importance is that, unlike British surgeons, the leading Japanese surgeons will not adopt new surgical practice as routine