Table 1. Trends of overall age-standardized incidence rates of lung cancer with joinpoint analyses in Japan and the United States

	Trend 1		Trend 2		Trend 3		Trend 4	
	Years	APC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)
Japan (1975–2003)								
Males & females	1975–1984	2.8[†] (2.0, 3.6)	1984–1993	1.5[†] (1.0–2.1)	1993–2003	0.0 (−0.3, 0.3)		
Males	1975–1992	2.2[†] (1.9, 2.5)	1992–2003	−0.6[†] (−0.9, −0.2)				
Females	1975–1982	3.6[†] (1.5, 5.8)	1982–2003	1.1[†] (0.9, 1.4)				
USA (1973–2005)								
Males & females	1973–1981	2.9[†] (2.4, 3.4)	1981–1991	0.7[†] (0.3, 1.0)	1991–2003	−1.3[†] (−1.5, −1.1)	2003–2005	−3.1[†] (−6.2, 0.0)
Males	1973–1981	1.8[†] (1.3, 2.2)	1981–1991	−0.6[†] (−1.0, −0.3)	1991–2003	−2.2[†] (−2.5, −2.0)	2003–2005	−4.5[†] (−8.0, 0.9)
Females	1973–1978	7.5[†] (5.6, 9.5)	1978–1988	3.9[†] (3.3, 4.4)	1988–1997	0.7[†] (0.2, 1.2)	1997–2005	−0.7[†] (−1.2, −0.3)

Source: SEER-9 areas covering about 10% of the US population (States of Connecticut, Hawaii, Iowa, Utah, and New Mexico, and the metropolitan areas of San Fransisco-Oakland, Detroit, Atlanta, and Seattle-Puget Sound), and Japanese nine areas covering about 10% of the Japanese population (Prefectures of Yamagata, Niigata, Fukui, Shiga, Osaka, Okayama, Saga and Nagasaki, Hiroshima City and Nagasaski City).
Joinpoint analyses with up to three joinpoints were based on rates (per 100,000 persons) and were age adjusted to the world population. Joinpoint analysis used the Joinpoint Regression Program, version 3.3. April 1, 2008, National Cancer Institute.
APC is based on rates that were age standardized to the world population.
[†]APC is statistically significantly different from zero (two-sided $p < 0.05$, calculated using a *t*-test).Abbreviations: APC: annual percent change; CI: confidence interval.

Figure 3. Joinpoint analysis of the age-standardized incidence rates (ASR) of lung cancer by histologic type among individuals in Japan and the United States. (*a*) Males and females combined Joinpoint analyses of the histology-specific ASR of lung cancer among individuals in Japan and in the United States are presented for (*a*) males and females combined, (*b*) males, (*c*) females. SQ, AD and SM indicate squamous cell carcinoma, adenocarcinoma and small cell carcinoma, respectively.

We used STATA version 10.1 (STATA Corporation, College Station, TX) for all analyses except the joinpoint regression analysis, for which we used the Joinpoint Regression Program version 3.3 (US National Cancer Institute, Bethesda, MD).

The Brown University Research Protections Office ruled that this study did not involve human subjects.

Results

Figure 1 illustrates temporal trends in annual nonfilter and filter cigarette consumption per capita in Japan and the United States. The sharp increase in filter cigarette consumption and sharp decrease in nonfilter consumption began in the 1960s and 1950s in the United States and Japan, respectively. Compared with the United States, the shift in consumption from nonfilter to filter cigarettes occurred more rapidly in Japan, with the share of filter cigarettes during this period rapidly reaching 99%. Further, the sharp increase in total consumption owed largely to increasing filter cigarette consumption. Filter cigarette consumption then generally continued to be flat until the late 1990s, when it began to

Table 2. Trends of age-standardized rates of lung cancer with joinpoint analyses by sex and histological group in Japan and the United States

Histology	Trend 1		Trend 2		Trend 3		Trend 4	
	Years	APC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)
Males & Females combined								
Japan (1975–2003)								
Squamous cell carcinoma	1975–1989	0.7† (0.2, 1.2)	1989–1992	4.4 (−3.3, 12.7)	1992–2003	−1.9† (−2.3, −1.4)		
Adenocarcinoma	1975–1990	2.4† (1.8, 3.0)	1990–1993	7.1 (−1.1, 15.9)	1993–2003	1.7† (1.1, 2.2)		
Small cell carcinoma	1975–1984	6.7† (4.2, 9.2)	1984–2003	0.2 (−0.6, 0.2)				
USA (1975–2003)								
Squamous cell carcinoma	1973–1982	2.1† (1.4, 2.8)	1982–1992	−1.7† (−2.4, −1.1)	1992–2005	−3.6† (−4.0, −3.2)		
Adenocarcinoma	1973–1978	9.4† (6.6, 12.3)	1978–1992	2.5† (2.4, 3.0)	1992–2005	−1.4† (−1.8, −1.0)		
Small cell carcinoma	1973–1981	6.4† (5.3, 7.6)	1981–1988	1.8† (0.4, 3.1)	1988–2005	−2.2† (−2.4, −1.9)		
Males								
Japan (1975–2003)								
Squamous cell carcinoma	1975–1994	1.7† (1.3, 2.1)	1994–2003	−2.4† (−3.1, −1.6)				
Adenocarcinoma	1975–1998	3.0† (2.7, 3.4)	1998–2003	0.2 (−1.6, 1.9)				
Small cell carcinoma	1975–1984	7.4† (4.4, 10.6)	1984–2003	−0.0 (−0.5, 0.5)				
USA (1973–2005)								
Squamous cell carcinoma	1973–1982	1.5† (0.7, 2.3)	1982–1992	−2.8† (−3.5, −2.1)	1992–2005	−4.5† (−4.9, −4.0)		
Adenocarcinoma	1973–1979	7.2† (5.7, 8.8)	1979–1992	1.4† (1.0, 1.8)	1992–1998	−1.3† (−2.6 − −0.0)	1998–2005	−3.3† (−4.1, −2.6)
Small cell carcinoma	1973–1980	6.2† (4.7, 7.7)	1980–1988	0.2 (−0.9, 1.3)	1988–2005	−3.1† (−3.4, −2.8)		
Females								
Japan (1975–2003)								
Squamous cell carcinoma	1975–2003	−1.4† (−1.8, −1.0)						
Adenocarcinoma	1975–2003	3.2† (2.9, 3.5)						

Epidemiology

decrease. In the United States, filter cigarette consumption peaked in the late 1970s.

Figure 2 and Table 1 provide the long-term trends in overall lung cancer incidence in Japan and the United States using the joinpoint regression analyses. For males and females combined, while the peak incidence has already occurred in the United States, with a downward trend beginning in 1991, the incidence for Japanese continues to be flat, followed by an upward trend until 1993. While the peak incidence for Japanese males occurred in 1992, the incidence for Japanese females continues to increase. Rates among Japanese males decreased by 0.6% per year from 1992 to 2003, after increasing by 2.2% annually from 1975 to 1992, and rates among Japanese females increased by 3.6% annually from 1975 to 1982 and by 1.1% after 1982. In the United States, peak incidence has already occurred in females in 1988, 7 years later than that in males. Among American males, rates decreased by 0.6% per year from 1981 to 1991 and by 2.2% per year from 1991 to 2005, after increasing by 1.8% annually from 1973 to 1978.

Figure 3 illustrates temporal patterns in ASR for selected histological types of lung cancer in Japan and the United States. For males and females combined (Fig. 3a), the peak incidence of SQ in Japanese occurred in 1992, 10 years later than that in the United States. In the United States, the rate of decline in SQ incidence significantly increased after 1992. While the incidence of AD continues to increase in Japan, peak incidence has already occurred in Americans, with a downward trend beginning in 1992. The incidence of AD in Japanese and Americans overtook the incidence of SQ in 1984 and 1976, respectively. For males (Fig. 3b), the peak incidence of SQs has already occurred in Japanese, with a downward trend beginning in 1994, 12 years later than that in the United States. While the incidence of AD for Japanese males leveled in 1998 after an upward trend, the peak incidence occurred in the US males, with a downward trend beginning in 1992. For females, the trends of SQ and AD in Japanese are different to those in Americans (Fig. 3c). In Japanese, the incidence for SQ continues to decrease and that for AD continues to increase. In contract, the peak incidences of SQ and AD have already occurred in 1982 and 1991 in the United States, respectively.

Table 2 provides the long-term trends in different histological groups of lung cancer incidence using the joinpoint regression analyses. For SQ, rates among Japanese increased by 0.7% annually from 1975 to 1989, were stable from 1989 to 1992, and then decreased by 1.9% from 1992 to 2003. Among Americans, rates increased by 2.1% annually from 1973 to 1982, then decreased by 1.7% from 1982 to 1992 and by 3.6% from 1992 to 2005. For AD, rates among Japanese increased by 2.4% annually from 1975 to 1990, were stable from 1990 to 1993 and then increased by 1.7% from 1993 to 2003. In contrast, rates among Americans increased by 9.4% annually from 1973 to 1978 and by 2.5% from 1978 to 1992 and then decreased by 2.2% from 1992 to 2005. In Japan,

Table 2. Trends of age-standardized rates of lung cancer with joinpoint analyses by sex and histological group in Japan and the United States (Continued)

Histology	Trend 1		Trend 2		Trend 3		Trend 4	
	Years	APC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)
Small cell carcinoma	1975–1982	8.7† (2.0, 15.7)	1982–2003	−1.6† (−2.3, −0.9)				
USA (1973–2005)								
Suamous cell carcinoma	1973–1984	5.3† (4.2, 6.3)	1984–1995	0.2 (−0.6, 1.1)	1995–2005	−2.5† (−3.3, −1.7)		
Adenocarcinoma	1973–1976	19.1† (9.5, 29.5)	1976–1991	4.2† (3.7, 4.7)	1991–2005	−0.3 (−0.7, 0.1)		
Small cell carcinoma	1973–1982	9.0† (7.2, 10.9)	1982–1991	2.7† (1.3, 4.1)	1991–2005	−1.6† (−2.1, 1.1)		

Source: SEER-9 areas covering about 10% of the US population (States of Connecticut, Hawaii, Iowa, Utah, and New Mexico, and the metropolitan areas of San Fransisco-Oakland, Detroit, Atlanta, and Seattle-Puget Sound), and Japanese nine areas covering about 10% of the Japanese population (Prefectures of Yamagata, Niigata, Fukui, Shiga, Osaka, Okayama, Saga and Nagasaki, Hiroshima City and Nagasaki City).

Joinpoint analyses with up to three joinpoints were based on rates (per 100,000 persons) and were age adjusted to the world population. Joinpoint analysis used the Joinpoint Regression Program, version 3.3.April 1, 2008, National Cancer Institute.

APC is based on rates that were age standardized to the world population.

†APC is statistically significantly different from zero (two-sided $p < 0.05$, calculated using a t-test.)

Abbreviations: APC: annual percent change; CI: confidence interval.

Table 3. The relationship between cigarette consumption and lung cancer incidence by histologic type in Japan and the United States

	SQ			AD		
Type of cigarette	Lag time τ^*	$\hat{\beta}_2^{SQ}$ ($\times 10^{-3}$)†	95% CI ($\times 10^{-3}$)	Lag time τ^*	$\hat{\beta}_2^{AD}$ ($\times 10^{-3}$)†	95% CI ($\times 10^{-3}$)
Japan						
Nonfilter	30	0.464‡	(0.164, 0.764)	24	−1.099‡	(−1.767 to −0.431)
Filter	30	−0.340‡	(−0.518, −0.162)	25	1.946‡	(1.297–2.594)
United States						
Nonfilter	20	0.455‡	(0.319, 0.591)	17	0.353	(−0.020 to 0.757)
Filter	25	−0.268‡	(−0.383–0.152)	15	3.183‡	(1.955–4.411)

*τ is defined as the lag between lung cancer incidence and cigarette consumption; CI, confidence interval. $^\dagger\beta_2$ is the coefficient for cigarette consumption in the model of $Y(t^+) = \beta_0 + \beta_1 Y(t) + \beta_2 X(t^+ - \tau) + \varepsilon$ ‡Statistically significantly different from zero (two-sided $p < 0.05$, calculated using a *t*-test).

rates for small cell carcinoma increased by 6.7% annually from 1975 to 1984, then leveled off thereafter. In contrast, rates in the United States increased by 6.4% annually from 1973 to 1981 and by 1.8% from 1981 to 1988, and then began to decrease thereafter.

Because sex-specific data on cigarette consumption by cigarette design were not available on public, we examined the relationship between cigarette consumption and lung cancer incidence by histologic type in males and females combined. Table 3 summarizes the statistical relationship between them using multiple regression analyses. The models in Table 3 did not violate assumptions of normality and uncorrelatedness. Among Japanese, the trend in nonfilter consumption was positively associated with the incidence of SQ ($\hat{\beta}_2^{SQ}$, 0.464×10^{-3}, 95% confidence interval (CI), [0.164×10^{-3}, 0.764×10^{-3}], $p = 0.006$) with the appropriate time lag of 30 years, and the trend in filter cigarette consumption was positively associated with AD incidence ($\hat{\beta}_2^{AD}$, 1.946×10^{-3}, 95%CI, [1.297×10^{-3}, 2.594×10^{-3}], $p < 0.001$) with the appropriate time lag of 25 years. Similarly, among Americans, the trend in nonfilter consumption was positively associated with SQ incidence ($\hat{\beta}_2^{SQ}$, 0.364×10^{-3}, 95%CI, [0.109×10^{-3}, 0.619×10^{-3}], $p = 0.008$) with the appropriate time lag of 20 years, while the trend in filter consumption was positively associated with AD incidence ($\hat{\beta}_2^{AD}$, 3.142×10^{-3}, 95%CI, [1.923×10^{-3}, 4.361×10^{-3}], $p < 0.001$) with the appropriate time lag of 15 years. The negative association between trends in nonfilter cigarette consumption and AD and between trends in filter consumption and SQ among Japanese and Americans reflect the shift in market share from nonfilter to filter cigarettes.

Discussion

AD has replaced SQ as the most frequent histologic type of lung cancer in both Japan and the United States. This increase in AD incidence in both the countries is also associated with the introduction of filtered cigarettes and the substantial increase in filter cigarette consumption. The decrease in nonfilter cigarette consumption due to the shift in market share from nonfilter to filter cigarette is associated with the decrease in the incidence of SQ. To our knowledge, these empirical observations, using population-based data from two distinct countries, are the first to support the long-held hypothesis that smoking filtered *vs.* nonfiltered cigarettes leads to separate presentations of lung cancer. These results are consistent with previous epidemiological study obtained using data at the individual level.[32–34]

Another possible explanation for the change in trends for AD of the lung is changes in exposure to air pollution. Long-term exposure to some components of polluted air, particularly NOx, might play a role in the development of AD.[12] Given that air pollution can be considered a general phenomenon, this possibility is not contradicted by the similarity in trends in AD incidence in US males and females but is contradicted by the difference in gender-specific trends in Japanese males and females. In addition, compared with current smokers, the lung cancer rate is very low among never smokers.[35] A prospective cohort study in Norway suggested that although air pollution is one of the causes of lung cancer, it may still much less than cigarette smoking that causes lung cancer.[36,37] A second possible explanation for this AD trend might be related to underlying trends in exposure to environmental tobacco smoke (ETS). Recent regulations have strictly reduced ETS exposure in the United States.[38] The consequent decrease in exposure to ETS might explain the recent decrease in incidence of ADs of the lung in the United States, at least, in part. Although this point should be examined in the future with more detailed exposure and outcome evaluation, it is clear that ETS has much less impact on the risk than active smoking.

Reflecting the wide-scale adoption of filter cigarettes beginning in the 1960s, the United States observed a sharp increase in ADs in the early 1970s, with 9.4% increases annually from 1973 to 1979. Interestingly, although filter cigarettes penetrated the Japanese market more rapidly in the 1970s, the increase in ADs in Japan has not been as sharp as in the United States. There are two explanations for this. First, the greater use of charcoal-containing cigarette filters in Japan (70 *vs.* 1% in the United States) may have had a beneficial effect, perhaps by trapping a greater load of fine particulates

than other filters or by removing a greater load of volatile toxic agents, such as hydrogen cyanide, N-nitrosamines and volatile aldehydes known to act as inhibitors of lung clearance.[19] In this regard, Muscat *et al.* found no association between charcoal filters and an attenuated risk of lung cancer in a Japanese population.[39] Second, it is of course also possible that the differences between the Japanese and US experience may have been affected by the assumptions used in allocating specific morphologies to cases of unknown morphology. Additional analyses focused on this issue may clarify the observed differences.

It is considered paradoxical that a proportion of Japanese who smoke is higher than American males but have a lower incidence of lung cancer.[19] Several factors acting either alone or in combination may explain this lower rate in Japan,[19,40] including age at onset of cigarette smoking, specific personal smoking (*i.e.*, manner of smoking, particularly shallow inhalation), and the contents and construction of cigarettes. Despite the higher smoking prevalence in Japan, total cigarette consumption per capita was lower than in the United States until 1987, suggesting that Japanese smokers smoked fewer cigarettes per day than their American counterparts. Other differences may explain the lower lung cancer rates in Japan: *e.g.*, because consumption of filter cigarettes increased rapidly around the same time that smoking became popular in Japan, Japanese smokers were less exposed to unfiltered cigarettes. Additionally, the Japanese diet may have a protective effect against lung cancer, owing to its relatively high consumption of soybeans,[41,42] which contain the strong tumor inhibitor genistein, and fish[41] and relatively low intake of dietary fat.[43] Frequent consumption of green tea[44] may also have a protective effect. Finally, Americans may have a greater genetic susceptibility to tobacco carcinogens than Japanese. In this regard, the lower relative risks by smoking in epidemiological studies conducted in Japan *versus* the United States is well known.[19,45] In this study, we found a shorter lag time of τ in Americans than in Japanese, which represents the shorter sum of induction and latent period in Americans than in Japanese (*e.g.*, lag times for AD after the advent of filter cigarettes were 25 years in Japan *vs.* 15 years in the United States). This might be a reflection of a difference in patterns of smoking behavior, life styles and susceptibility to lung cancer between Japan and the United States.

Our findings suggest that the trends of incidence of lung cancer by histologic type differ in males and females as well as the associations between changes in the incidences and in filter/nonfilter cigarettes differ among males and females, in both Japan and in the United States. That may be due to the differences in patterns of smoking behavior and the susceptibility to lung cancer in cigarette smokers among males and females. Smoking rate is significantly lower for females than for males in both the countries (11.0 and 39.4% in males and females in Japan, respectively, and 17.4 and 23.4% in the United States).[27,46] Females were more likely than men to smoke filter cigarettes (89.0–90.6% *vs.* 75.0–79.3% in the 1970s,[47,48] and 92.9–94.6% *vs.* 87.0–90% in the 1980s). Females with lung cancer are more likely to be never smokers or less intense smoking history, and have AD subtypes.[49] Therefore, the sex-specific analysis for cigarette types and incidence patterns by histology subtype would sharpen the findings. However, unfortunately, the data on filter/nonfilter cigarette consumption are not available both in Japan and the United States so that we could not analyze the sex specific relationships between the trend in lung cancer incidence by histologic type and consumptions of filter or nonfilter cigarettes. Therefore, the analyses in males and females combined may weaken a true relationship between the increased trend in AD and filter cigarette consumption. Nevertheless, we could obtain the statistically significant relationship between them using the data for males and females combined.

Molecular examinations of lung cancer might give us an insight to interpret different patterns of change in histology-specific incidence by sex and ethnicities discussed above. It has been reported that epidermal growth factor receptor (*EGFR*) mutations commonly present in female, never-smoker and Asian ethnicity.[50] Potential differences in several risk factors including smoking by *EGFR* mutational status have been reported to date.[51,52]

Several limitations of this study warrant mention. First, as an ecological study, it possesses all the limitations inherent to ecological analyses. Aggregate data on exposure and disease—data obtained from population aggregates—cannot be linked to individuals. Although estimated consumption of cigarettes was based on nationally averaged levels for the respective countries, consumption may in fact vary by area (rural *vs.* metropolitan), race/ethnicity, sex, age and education. The increased consumption of filter cigarettes may have played different roles in the increase in AD incidence in males and females, but the present data lacked the sensitivity to detect changes at this level. Second, the data collected from Japanese prefectural population-based cancer registries have major quality issues and fail to meet international data quality standards for the proportion of death-certificate-only cases, incidence-to-mortality ratio and proportion of histologically verified cases.[53] Based on mathematical modeling, true incidence may be underestimated by as much as 20%.[54] Moreover, because one-third of the Japanese cases in this study were of unknown morphology, the data may not adequately reflect the true changes in lung cancer incidence by histologic type. Nevertheless, we do not consider that our allocation methodology biased the results, and reanalysis of the data without the proportional reallocation of cases with unspecified morphology returned virtually identical results. Finally, another limitation may be change over time in the definition of AD[55] or in diagnostic practice,[56] although we consider that these themselves cannot account for the increase in AD incidence. For example, major diagnostic advances such as bronchoscopy, thin-needle aspiration, computed tomography scans

and improved stains for mucin were all introduced in the 1980s,[56] after the increases in the incidence of AD were observed.

While the decreased incidence of SQ among Japanese and Americans is encouraging in terms of cancer prevention and control, it is counterbalanced by the increases in AD, especially among Japanese. As realization of the detrimental health effects of cigarette smoking initially grew, the tobacco industry strove to develop filtered cigarettes as less harmful cigarettes, but subsequent scientific evidence has failed to demonstrate any benefit from changes in cigarette design or manufacturing.[57] Despite the tobacco industry became well aware of the fact that filtered cigarettes were not less harmful, it has been advertised filtered or low-tar cigarettes to intend to reassure smokers and were meant to prevent smokers form quitting since the early 1950s in the United States[58] and later in Japan.[59] The false reassurances provided by marketing strategies of filtered/low-tar cigarettes might be related to the rising incidence of ADs of the lung.

The present results suggest that the shift from nonfilter to filter cigarettes may have had the result of replacing one cancer type with another. These findings emphasize the importance of tobacco control programs, namely programs that prevent the initiation of smoking, hasten the rate of smoking cessation or limit exposure to ETS, have been associated with a decrease in both cigarette consumption and smoking rates, and subsequently with a decrease in lung cancer incidence.[4,60]

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OVERVIEW

Strategies for Cancer Control on an Organ-Site Basis

Malcolm A Moore[1,2], Tomotaka Sobue[2]

Abstract

A great deal of research information has been generated regarding cancer incidence rates and underlying risk factors. Since incidence:mortality ratios are generally less than 2:1 and often approach equivalence there clearly is a need for particular emphasis on preventive measures and early detection. Whether the latter should be through screening or education for improved awareness will depend on the socioeconomic conditions and the organ site. The location within the body, physiological factors and the cell type, whether essentially glandular or squamous, and the particular risk and protective factors operating in the particular social context will all impact on what measures can be recommended. Here the focus is on primary and secondary prevention of cancers in the various regions of Asia, taking into account similarities and differences in etiology for organs/tisssues of the gastrointestinal tract, the respiratory tract, the urinary system, the reproductive system, the nervous system, the thyroid and non-Hogkins lymphomas and leukemias. Globocan 2002 data on incidence and mortality and all of the findings reviewed in the Regional Reviews were taken into account in compiling this overview. The chief recommendations are education in the developing world, to overcome the problem of late presentation at hospital (reflected by high mortality/incidence ratios), betel and tobacco control for the oral cavity and pharynx, reduce salt intake and targeting of *Helicobacter pylori* for the stomach, reduction in food intake, improvement in the diet and more exercise for the colorectum, kidney, prostate, breast, ovary and endometrium, reduction in smoking and exposure to other fumes for the lung, increase in water intake, particularly for the urinary bladder, and avoidance of parasites for the special cases of the urinary bladder and intrahepatic bile ducts. The cancer registry could be a major resource for development of further research capacity, with selection of suitable partners in areas with contrasting cancer rates and lifestyles for detailed comparisons applying the same protocols. This should facilitate future exploration and hopefully elucidation of any anomalies, so that cancer control programs can be optimized in accordance.

Asian Pacific J Cancer Prev, **10,** Asian Cancer Epidemiology Supplement, 149-164

Introduction

The prevailing view is that the majority of cancers are due, very largely, to the environment, with only some 5-10% being primarily related to genetic abnormalities. Naturally, the genetic backgound does play many roles, but this is in the context of interactions with the major environmental factors, whether they be chemical or other types of carcinogenic agents, or causes of inflammation and cell proliferation. This is in line with the initiation-promotion paradigm, whereby neoplasia is 'initiated' at the single cell level (a so-called 'field' effect arising when many cells are hit) by exposure to an agent capable of causing genetic alteration, which can be 'fixed' on cell division, and then 'promoted' by influences which result in growth of initiated populations to form preneoplasias, precancers and eventually malignancies (see Figure 1).

Primary prevention concerns measures aimed at reducing carcinogen initiation and actions during the phase before focal lesions become apparent, including education for awareness of risk factors, tobacco control and lifestyle changes to reduce inflammatory proliferation pressure. Since both harmful and beneficial factors exist, the term chosen here is 'modulation'. Secondary prevention then covers screening and early detection, along with education to help ensure that patients comply with screening guidelines and present for treatment as soon as symptoms develop.

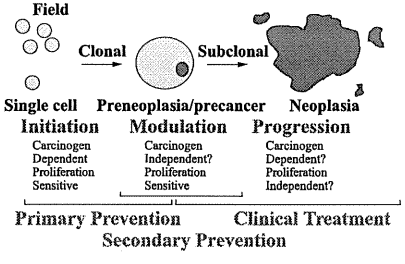

Figure 1. Processes in Neoplasia and Prevention

For cancer control there are clearly measures which will impact on all locations in the body, like reduction in tobacco consumption and therefore carcinogen exposure, but this will have differing degrees of influence depending on the organ site. Adjacent or related structures may clearly be affected by the same factors, but at the same time may react differently because of other, sometimes conflicting, influences. In the treatment given below we therefore consider the major organ systems as wholes before going on to the individual tissue sites in discussion.

The Gastrointestinal Tract

Stretching from the lips to the anus, the alimentary tract accounts in total for more than half the cancers in most male populations and about one quarter in females. The lining epithelium is squamous to the junction of the oesophagus and stomach, then presenting as highly differentiated glandular elements through to the anus, where a second transition back to squamous is found. Relationships between estimated incidence rates for pairs of sites in Asian countries are illustrated in Figure 2. For the purpose of these comparisons, division is into regions, Singapore being exceptionally assigned to the North-East region because of the predominately Chinese population.

Despite the shared histology, there are no clear links among oral, pharyngeal and oesophageal cancers overall, although South Asia tends to have relatively high incidences of all three. Some Pacific islands have very prominent oral cancers but neither of the others. North-West and North-East Asia both have high shared oesophageal and stomach cancer incidences. Neither of these latter appear to have any link to colorectal cancer.

Oral Cavity

The Globocan 2002 mortality/incidence data for the oral cavity are plotted in Figure 3. The average ratio is 0.5:1, with very little variation across countries. Males are generally more than twice as likely as females to be effected, although Bangladesh would appear to be exceptional, with similar rates in both sexes, and Sri Lanka

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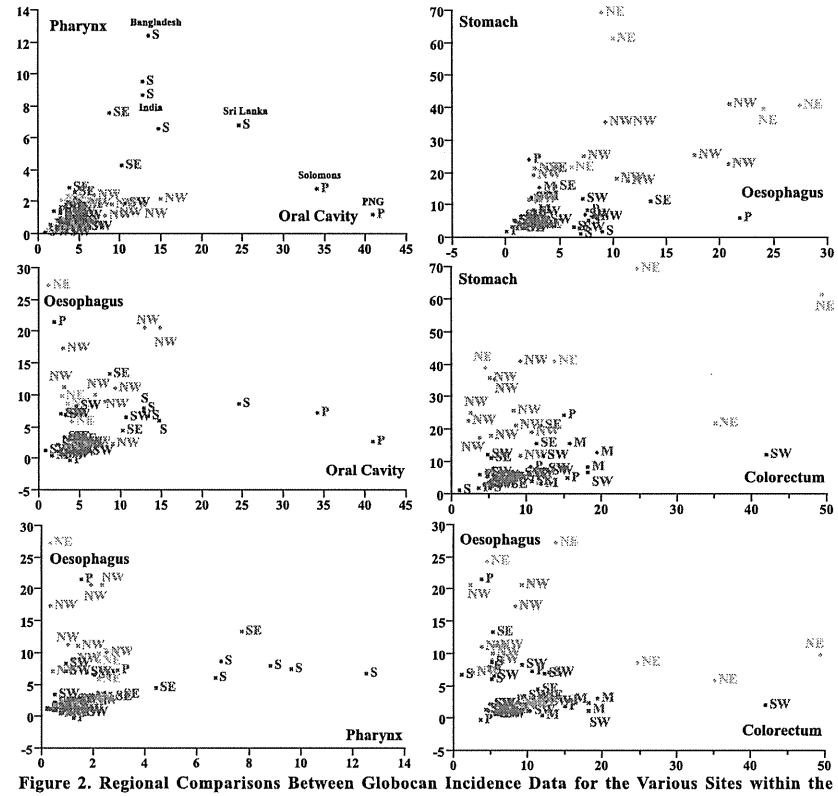

Figure 2. Regional Comparisons Between Globocan Incidence Data for the Various Sites within the Gastrointestinal Tract (M, Southeast, Peninsular and Island; NE, Northeast; NW, Northwest; P, Pacific; SE, Southeast Mainland; SW, Southwest)

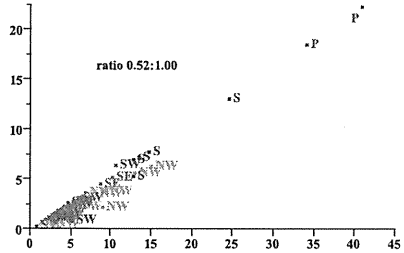

Figure 3. Mortality/Incidence Data for the Oral Cavity (Globocan 2002; Ferlay et al., 2004)

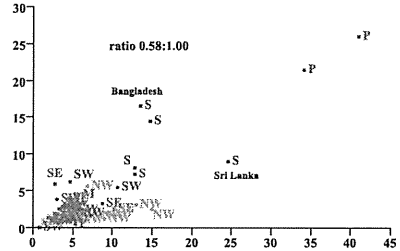

Figure 4. Female/Male Incidence Data for the Oral Cavity (Globocan 2002; Ferlay et al., 2004)

has a particularly strong male predominance (see Figure 4). Underlying causes are unclear and if real this warrants investigation.

Evidence for risk and protective factors from Asia, detailed in the separate regional sections of this supplement, is summarized in Table 1. Those which obviously need to be avoided as a preventive measure (see Figure 5) are betel chewing and tobacco. Given the role for tobacco, for *a priori* reasons vegetables should be protective, as concluded by the WCRF/AICR (2007), but there is only limited information available in Asia. Alcohol is not a major influence in the very high risk populations of South Asia but could be playing a role elsewhere, like in the Pacific and North. Very hot drinks may confer some risk, as do other sources of trauma, including salt and grit, and deficiency in zinc or other metals in the diet. These factors all impact on squamous cell carcinoma development. In the adenocarcinoma case, obesity is the main risk determinant.

Table 1. Asian Evidence for Modifying Factors for the Oral Cavity

	NW	SW	S	SEM	SEI	Pac	NE	World*
Prevalence	L	L-M	H	L-M	L	L-H	L	NA
Lifestyle								
Tobacco	++	++	+++	+	ND	++	++	NA
Reverse smoking	ND	ND	ND	ND	+	ND	ND	NA
Alcohol	+/-	ND	-	-	ND	-	++	+++
Betel	ND	ND	+++	+++	+	++	+	NA
Diet								
Hot Drinks	ND	ND	ND	ND	ND	ND	ND	+
Vegetables	ND	ND	ND	ND	ND	ND	ND	--#
Fruits	ND	ND	ND	ND	ND	ND	ND	--
Coffee	ND	ND	ND	ND	ND	ND	-	+/-

*World Cancer Research Fund,American Institute for Cancer Research 2007; NW, North-West, SW, South-West, S, South; SEM, South-East Mainland; SEI, South-East Island; Pac, Pacific; NE, North-East; L, low; M, medium;, H, high; NA, not applicable; ND, no data; -/--, slight/weak protection, +/-, no effect, +/++/+++, slight, weak, strong risk #Carotenoids

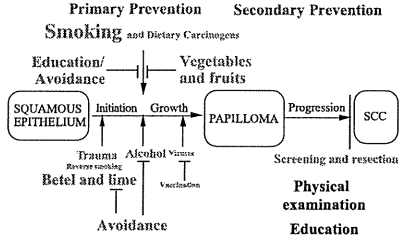

Figure 5. Prevention Measures for the Oral Cavity

in the Pacific and North. There is limited evidence of protection by coffee drinking. while hot drinks may confer some risk.

Regarding secondary prevention, there has been one randomized clinical trial which provided evidence of efficacy of oral examination, so that use of trained workers for screening of high risk groups can be recommended.

Oesphagus

The Globocan 2002 mortality/incidence data for the oral cavity are plotted in Figure 6. The average ratio is 0.8:1, with possible slightly better results for China, Mongolia and Kazakhstan. Whether this is real requires confirmation. Males are generally more than twice as like as females to be effected, although in Japan and China the male predominance is much more marked (see Figure 7). In contrast, Sri Lanka has almost equal values for the

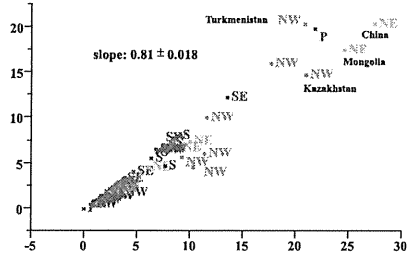

Figure 6. Mortality/Incidence Data for the Oesophagus (Globocan 2002; Ferlay et al., 2004)

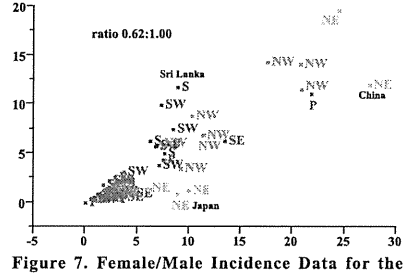

Figure 7. Female/Male Incidence Data for the Oesophagus (Globocan 2002; Ferlay et al., 2004)

Table 2. Asian Evidence for Modifying Factors for the Oesophagus

	NW	SW	S	SEM	SEI	Pac	NE	World*
Prevalence	L-H	L	M	L-M	L	L-H	L	NA
Lifestyle								
Carcinogens	ND	ND	ND	ND	ND	ND	+	NA
Tobacco	++	++	+++	+	ND	ND	++	NA
Alcohol	+/-	ND	-	+	ND	ND	++	+++
Betel	ND	ND	++	+	ND	ND	+	NA
Obesity	ND	ND	ND	ND	ND	ND	+#	+++#
Diet								
Deficiency	++	ND	+	ND	ND	ND	++	+
Hot Drinks	++	ND	ND	ND	ND	ND	+	+
Vegetables	ND	ND	-	ND	ND	ND	--	--
Fruits	ND	ND	-	ND	ND	ND	-	--
Meat	ND	ND	ND	ND	ND	ND	ND	+
Salt	+	ND	ND	ND	ND	ND	+	+/-
Tea	ND	ND	ND	ND	ND	ND	-	+/-

*World Cancer Research Fund,American Institute for Cancer Research 2007; NW, North-West, SW, South-West, S, South; SEM, South-East Mainland; SEI, South-East Island; Pac, Pacific; NE, North-East; L, low; M, medium;, H, high; NA, not applicable; ND, no data; -/--, slight/weak protection, +/-, no effect, +/++/+++, slight, weak, strong risk; # for adenocarcinomas

two genders. In fact, the major variation points to opportunities for collaborative research, taking into account relative rates for adenocarcinomas.

Evidence for risk and protective factors from Asia is summarized in Table 2. The obvious factors which need to be avoided as a preventive measure (see Figure 8) are tobacco, and to a much lesser extent betel chewing. For *a priori* reasons, again vegetables should be protective, as concluded by the WCRF/AICR (2007), but once more data from Asia are limited. However, there are sufficient to allow recommendation of vegetable and fruit intake. Alcohol is not a major influence in the very high risk populations of South Asia but could be playing a role elsewhere, like in the Pacific and North. Very hot drinks may confer some risk, as do other sources of trauma, including salt and grit, and deficiency in zinc or other metals in the diet. These factors all impact on squamous cell carcinoma development. In the adenocarcinoma case, obesity is the main risk determinant.

For secondary prevention there are no specific screening measures which can be advised other than increase in general awareness of symptoms.

Stomach

The Globocan 2002 mortality/incidence data for the

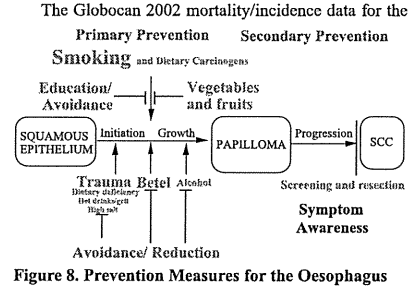

Figure 8. Prevention Measures for the Oesophagus

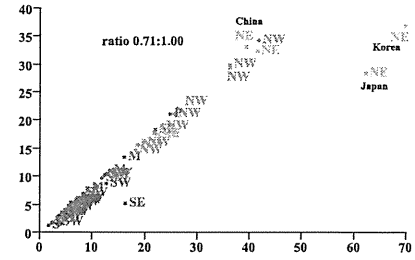

Figure 9. Mortality/Incidence Data for the Stomach (Globocan 2002; Ferlay et al., 2004)

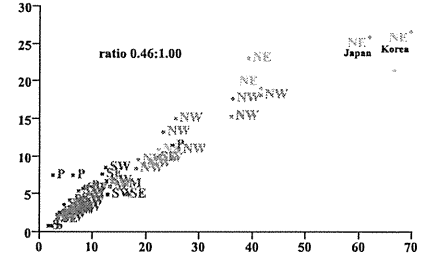

Figure 10. Female/Male Incidence Data for the Stomach (Globocan 2002; Ferlay et al., 2004)

stomach are plotted in Figure 9. The average ratio is 0.7:1, with Korea and Japan in the high risk countries exhibiting an appreciably better outcome, than in China for example. How much of this due to screening needs to be clarified. Males are generally more than twice as likely as females to be effected, and in Japan and Korea the predominance is slightly more marked (see Figure 10). Data on the relative prevalences of different sites with their variation

Table 3. Asian Evidence for Modifying Factors for the Stomach

	NW	SW	S	SEM	SEI	Pac	NE	World*
Prevalence	L-H	L	L	L-M	L	L-H	L	NA
Lifestyle								
Helicobacter	++	ND	+	ND	++	ND	++	NA
Tobacco	ND	ND	+/-	ND	+	ND	++	NA
Alcohol	ND	ND	+/-	ND	ND	ND	+	+/-
Obesity	ND	ND	ND	ND	ND	ND	+	+/-
Exercise	ND	ND	ND	ND	ND	ND	-	+/-
Diet								
Vegetables	ND	ND	-	-	--	ND	--	--
Fruits	ND	ND	-	-	-	ND	-	--
Meat	ND	ND	ND	ND	ND	ND	ND	+
Fish	ND	ND	ND	ND	ND	ND	--	+
Smoked food	ND	ND	ND	ND	ND	ND	+	+
Salt	ND	ND	ND	++	++	ND	++	++
Coffee	ND	ND	ND	ND	ND	ND	-	+/-

*World Cancer Research Fund,American Institute for Cancer Research 2007; NW, North-West, SW, South-West, S, South; SEM, South-East Mainland; SEI, South-East Island; Pac, Pacific; NE, North-East; L, low; M, medium;, H, high; NA, not applicable; ND, no data; -/--, slight/weak protection, +/-, no effect, +/++/+++, slight, weak, strong risk

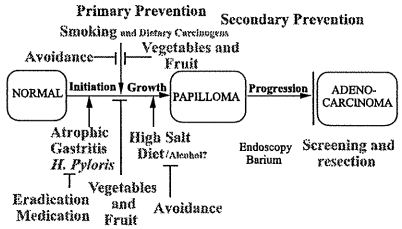

Figure 11. Prevention Measures for the Stomach

in risk factors are lacking, although it is possible that a combination of diet and tobacco might explain the gender effect.

Evidence for risk and protective factors from Asia is summarized in Table 3. The obvious factors which need attention in preventive measures (see Figure 11) are heavy infection with *Helicobacter pylori* and high salt intake. Tobacco should also be avoided, while consumption of vegetables and fruits can be recommended. Alcohol is not a major influence

Regarding secondary prevention, there is ample evidence of efficacy for screening.

Colon and Rectum

The Globocan 2002 mortality/incidence data for the colo-rectum are plotted in Figure 12. The average ratio is over 0.5:1, with Japan, Israel and Korea demonstrating appreciably better outcomes, possibly linked to screening. This might be supported by the fact that Singapore has

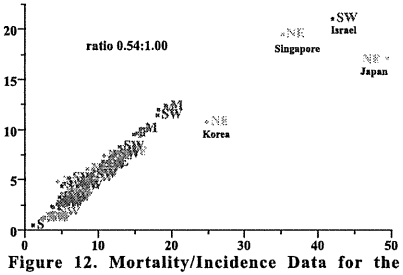

Figure 12. Mortality/Incidence Data for the Colorectum (Globocan 2002; Ferlay et al., 2004)

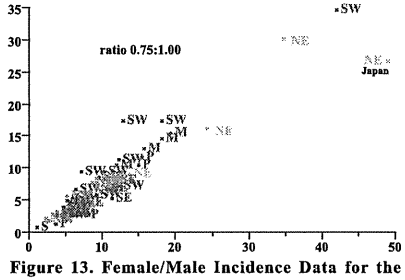

Figure 13. Female/Male Incidence Data for the Colorectum (Globocan 2002; Ferlay et al., 2004)

Table 4. Asian Evidence for Modifying Factors for the Colorectum

	NW	SW	S	SEM	SEI	Pac	NE	World*
Prevalence	L-M	L-H	L	L-M	M	L-H	L	NA
Lifestyle								
Carcinogens	ND	+	ND	ND	+	ND	+	NA
Tobacco	ND	ND	ND	ND	+	ND	+	NA
Alcohol	ND	ND	ND	ND	ND	ND	+	+++
Obesity	ND	ND	ND	ND	ND	ND	+	+++
Exercise	ND	ND	ND	ND	ND	ND	--	---
Diet								
Vegetables	ND	-	ND	-	--	ND	--	--
Fruits	ND	-	ND	-	-	ND	-	-
Fat	ND	ND	ND	ND	ND	ND	++	+
Sugar	ND	ND	ND	ND	ND	ND	ND	+
Meat	ND	ND	ND	+	+	ND	+	+++
Fish	ND	ND	ND	ND	ND	ND	--	-
Milk	ND	ND	ND	ND	ND	ND	ND	--
Tea	ND	ND	ND	ND	ND	ND	-	NA

*World Cancer Research Fund,American Institute for Cancer Research 2007; NW, North-West, SW, South-West, S, South; SEM, South-East Mainland; SEI, South-East Island; Pac, Pacific; NE, North-East; L, low; M, medium;, H, high; NA, not applicable; ND, no data; -/--, slight/weak protection, +/-, no effect, +/++/+++, slight, weak, strong risk

an only slightly better rate. Males are generally 1.25 more likely than females to be effected (see Figure 13), but in Japan the figure is nearer 2.0, pointing to a possible role for alcohol and smoking.

Evidence for risk and protective factors from Asia is summarized in Table 4. The obvious factors which need to be avoided as preventive measures (see Figure 14) are obesity and excessive alcohol consumption. Furthermore a diet high in meat and fat is detrimental, while consumption of vegetables and fish as well as physical exercise are protective. Tobacco and dietary carcinogens may be secondary risk factors.

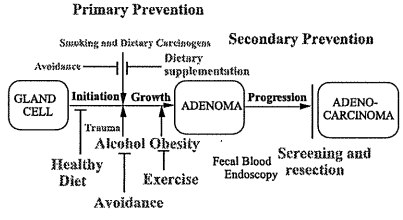

Figure 14. Prevention Measures for the Colorectum

Regarding secondary prevention, there is strong evidence for the efficacy of occult blood based approaches, along with endoscopy and computed tomography in the future.

The Hepatopancreatic Axis

The liver, gallbladder and pancreas form the hepatopancreatic axis, closely juxtaposed and related in many functions. They give rise to hepatocellular carcinomas from hepatocytes and adenocarcinomas from ductal and ductular cell populations (cholangiocarcinomas in the intra- and extra- hepatic bile duct cases). There are conceivable shared risk factors and a comparison of

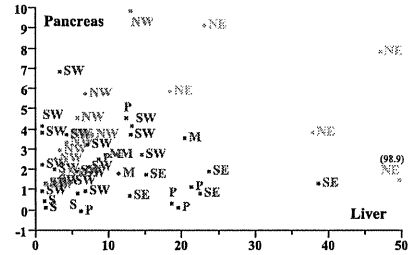

Figure 15. Regional Comparisons Between Globocan Incidence Data for the Liver and Pancreas

Globocan incidence data for the liver and pancreas is shown in Figure 15. While Japan and Korea have relatively high incidences of both, pancreas incidences are generally low, North- and South-West populations tending to have relatively greater values than their South-East and Pacific counterparts.

Liver

The Globocan 2002 mortality/incidence data for the liver are plotted in Figure 16. Survival is very poor, with Korea demonstrating the best M/I ration of 0.76:1. Whether this is a reflection of screening activity needs to be clarified. Males in general are more than twice as likely as females to be effected, and in Korea the predominance is more marked (see Figure 17). Therefore, male factors like alcohol and smoking presumably must interact with the primarily viral etiology. There in fact appears to be

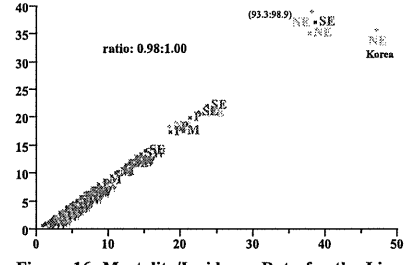

Figure 16. Mortality/Incidence Data for the Liver (Globocan 2002; Ferlay et al., 2004)

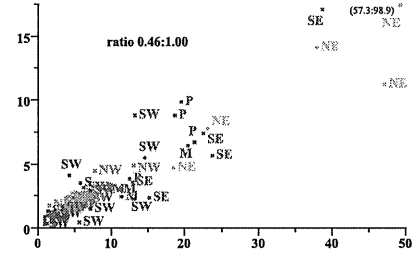

Figure 17. Female/Male Incidence Data for the Liver (Globocan 2002; Ferlay et al., 2004)

Table 5. Asian Evidence for Modifying Factors for the Liver

	NW	SW	S	SEM	SEI	Pac	NE	World*
Prevalence	L-M	L-M	L	M-H	M-H	L-H	H	NA
Lifestyle								
Viruses	++	++	++	++	++	++	+++	NA
Parasites#	ND	ND	ND	+++	ND	ND	+	NA
Carcinogens	ND	+	ND	ND	ND	ND	++	+++
Tobacco	ND	ND	ND	ND	ND	ND	++	NA
Alcohol	+	ND	ND	ND	ND	ND	++	++
Obesity	+	ND	+	ND	ND	ND	+	+/-
Exercise	ND	ND	ND	ND	ND	ND	--	+/-
Diet								
Vegetables	ND	ND	ND	ND	ND	ND	--	+/-
Fruits	ND	ND	ND	ND	ND	ND	-	-
Fat	ND	ND	ND	ND	ND	ND	++	+/-
Fish	ND	ND	ND	ND	ND	ND	-	+/-
Soy	ND	ND	ND	ND	ND	ND	-	+/-
Coffee	ND	ND	ND	ND	ND	ND	-	NA

*World Cancer Research Fund,American Institute for Cancer Research 2007; NW, North-West, SW, South-West, S, South; SEM, South-East Mainland; SEI, South-East Island; Pac, Pacific; NE, North-East; L, low; M, medium;, H, high; NA, not applicable; ND, no data; -/--, slight/weak protection, +/-, no effect, +/++/+++, slight, weak, strong risk; for cholangiocellular liver cancers

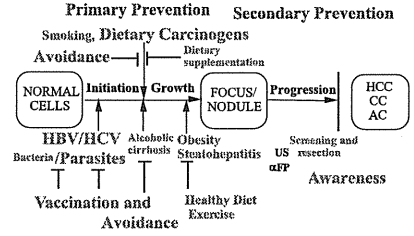

Figure 18. Cancer Prevention and Control for the Liver and Gallbladder Cancer

considerable variation in the sex ratio with the South-West populations, which remains to be explained.

Evidence for risk and protective factors from Asia is summarized in Table 5. The obvious factors which need to be avoided as a preventive measure (see Figure 18) are carcinogen exposure and viral and parasite infection, with lesser roles for alcohol and tobacco. Vegetables and other dietary influences are generally protective. Due to the link with steatohepatitis, avoidance of overweight may also be recommended.

Although ultrasound and serum markers may be useful for high risk individuals, there are no population level screening measures so that secondary prevention is generally limited to awareness of symptoms.

Gallbladder

The gallbladder is not included in Globocan 2002 so that mortality/incidence data are not available. From the available population-based registry data, there is generally a female predominance, which is pronounced in some of the South Asian registries. The main risk factor is obesity, with a possible role for bacterial infection, especially with *Salmonella*, and gallstones.

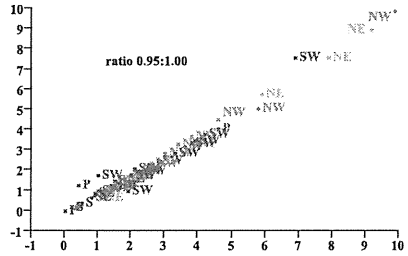

Figure 19. Mortality/Incidence Data for the Pancreas (Globocan 2002; Ferlay et al., 2004)

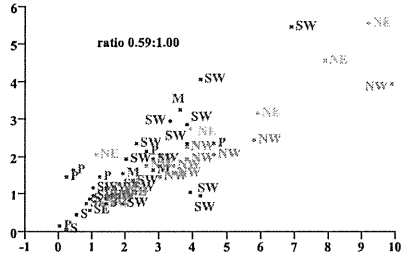

Figure 20. Female/Male Incidence Data for the Pancreas (Globocan 2002; Ferlay et al., 2004)

Table 6. Asian Evidence for Modifying Factors for the Pancreas

	NW	SW	S	SEM	SEI	Pac	NE	World*
Prevalence	L-M	L-M	L	L-M	L-M	M-H	L-H	NA
Lifestyle								
Carcinogens	ND	+	ND	ND	ND	ND	ND	+/-
Tobacco	++	++	ND	ND	ND	ND	++	NA
Alcohol	ND	ND	ND	ND	ND	ND	++	++
Obesity	ND	+	ND	ND	ND	ND	++	+++
Exercise	ND	ND	ND	ND	ND	ND	ND	-
Diet								
Vegetables	ND	ND	ND	ND	ND	ND	--	--
Fruits	ND	ND	ND	ND	ND	ND	-	-
Meat	ND	ND	ND	ND	ND	ND	ND	+
Coffee	ND	ND	ND	ND	ND	ND	-	+/-

*World Cancer Research Fund,American Institute for Cancer Research 2007; NW, North-West, SW, South-West, S, South; SEM, South-East Mainland; SEI, South-East Island; Pac, Pacific; NE, North-East; L, low; M, medium;, H, high; NA, not applicable; ND, no data; -/--, slight/weak protection, +/-, no effect, +/++/+++, slight, weak, strong risk

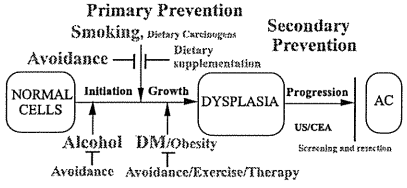

Figure 21. Cancer Prevention and Control for Pancreatic Cancer

Pancreas

The Globocan 2002 mortality/incidence data for the pancreas are plotted in Figure 19. The ratio is almost:1:1, with no exception. Males are generally more than twice as like as females to be effected, but there is considerable variation in the gender ratios (see Figure 7), which might reflect tobacco and alcohol consumption patterns to some extent.

Evidence for risk and protective factors from Asia is summarized in Table 6. The obvious factors which need to be avoided as a preventive measure (see Figure 21) are alcohol, tobacco and obesity/diabetes mellitus. Vegetables are protective, along with coffee drinking, while meat consumption may confer some risk.

Regarding secondary prevention, there are no population based measures to be recommended.

The Respiratory Tract

The respiratory tract comprises the pharynx (including the nasopharynx), the larynx and the lung. In all cases where the epithelium is squamous the SCC is the major cancer. With the lung, adenocarcinomas of the periphery and small and large cell cancers are also found, but no distinction was made in Globocan 2002. Correlations between sites are shown in Figure 22. The South Asian countries, as well as Mynamar, generally feature high rates for both the pharynx and larynx, but elsewhere pharyngeal incidences are low, independent of the laryngeal cancer prevalence. The lung and larynx, in contrast, show a tendency to increase in parallel, although the South and South-West have relatively more laryngeal, the South-East and North-East has more lung and the North-West is intermediate.

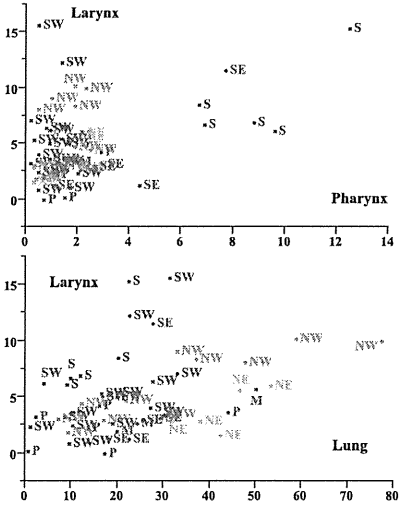

Figure 22. Regional Comparisons Between Globocan Incidence Data for the Pharynx, Larynx and Lung

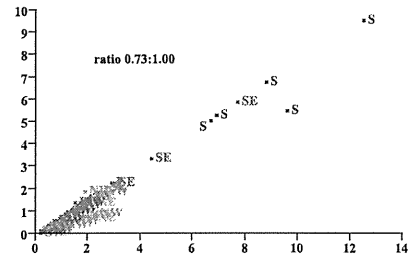

Figure 23. Mortality/Incidence Data for the Pharynx (Globocan 2002; Ferlay et al., 2004)

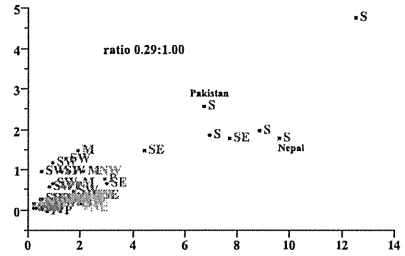

Figure 24. Female/Male Incidence Data for the Pharynx (Globocan 2002; Ferlay et al., 2004)

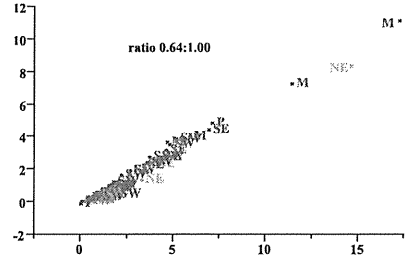

Figure 25. Mortality/Incidence Data for the Nasopharynx (Globocan 2002; Ferlay et al., 2004)

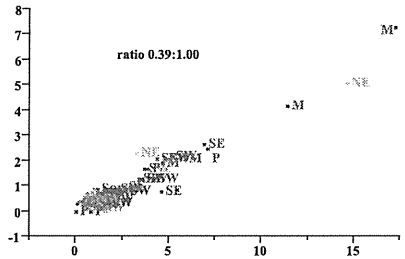

Figure 26. Female/Male Incidence Data for the Nasopharynx (Globocan 2002; Ferlay et al., 2004)

Table 7. Asian Evidence for Modifying Factors for the Pharynx and Larynx

	NW	SW	S	SEM	SEI	Pac	NE	World*
Prevalence	L-H	L-H	M-H	L-M	L-M	M-H	L-M	NA
Lifestyle								
Tobacco	+	ND	++	ND	++	ND	++	NA
Herbs#	ND	ND	ND	ND	+	ND	ND	NA
Alcohol	+	ND	ND	ND	ND	ND	++	+++
Dusts	++	ND	ND	ND	ND	ND	++	NA
Hot drinks	ND	ND	ND	ND	ND	ND	ND	+
Diet								
Vegetables	ND	ND	ND	ND	ND	ND	--	---
Fruits	ND	ND	ND	ND	ND	ND	-	---
Salt#	ND	ND	ND	ND	ND	ND	++	+/-
Coffee	ND	ND	ND	ND	ND	ND	-	+/-

*World Cancer Research Fund,American Institute for Cancer Research 2007; NW, North-West, SW, South-West, S, South; SEM, South-East Mainland; SEI, South-East Island; Pac, Pacific; NE, North-East; L, low; M, medium;, H, high; NA, not applicable; ND, no data; -/--, slight/weak protection, +/-, no effect, +/++/+++, slight, weak, strong risk;# for the nasopharynx

Pharynx, Nasopharynx and Larynx

The Globocan 2002 mortality/incidence data for the pharynx are plotted in Figure 23. The average ratio is 0.7:1, with slightly better outcomes apparently in India. Whether this is real requires confirmation. Males are three times more likely than females to be effected, and this gender bias may be more marked in Nepal (see Figure 24).

The Globocan 2002 mortality/incidence data for the nasopharynx are plotted in Figure 25, with an average

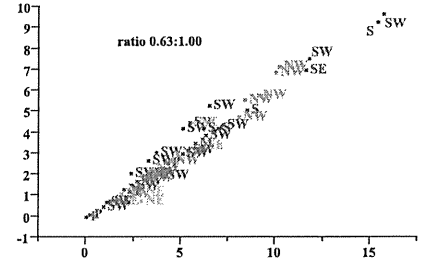

Figure 27. Mortality/Incidence Data for the Larynx (Globocan 2002; Ferlay et al., 2004)

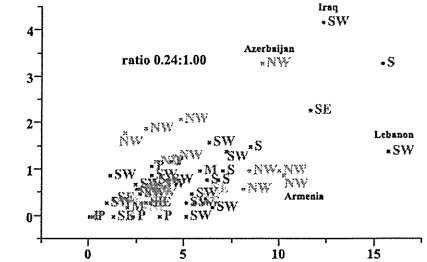

Figure 28. Female/Male Incidence Data for the Larynx (Globocan 2002; Ferlay et al., 2004)

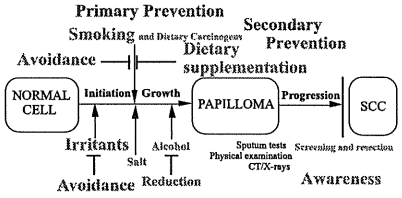

Figure 29. Cancer Prevention and Control Measures for the Pharynx and Larynx

ratio 0.64:1,and the gender distibution is shown in Figure 26) again males having approximately three times the rates of females. In the larynx the situation is similar (Figures 27 and 28), but here there is marked variation in rates for males and females between different countries in the same region, as for example with neighbouring Azerbaijan and Armenia.

Evidence for risk and protective factors for the pharynx and larynx from Asia is summarized in Table 7. The obvious factors which need to be avoided as a preventive measure (see Figure 29) are tobacco dusts (mainly for the larynx) and to a lesser extent alcohol. Both vegetables and fruits are clearly strongly protective, and coffee weakly so. Salty foods are risk factors for the nasopharynx.

There are no secondary prevention measure that can currently be recommended.

Lung

The Globocan 2002 mortality/incidence data for the

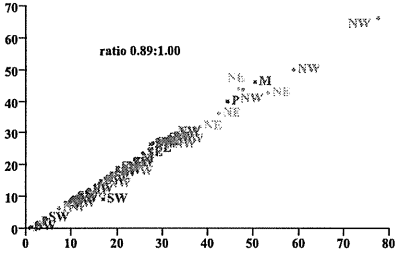

Figure 30. Mortality/Incidence Data for the Lung
(Globocan 2002; Ferlay et al., 2004)

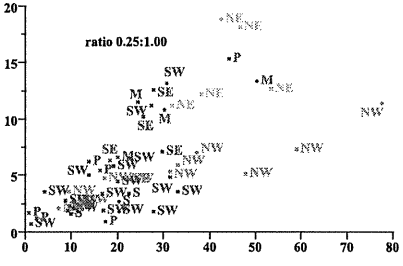

Figure 31. Female/Male Incidence Data for the Lung
(Globocan 2002; Ferlay et al., 2004)

Table 8. Asian Evidence for Modifying Factors for the Lung

	NW	SW	S	SEM	SEI	Pac	NE	World*
Prevalence	L-H	L-M	L-M	L-M	L-H	M-H	M-H	NA
Lifestyle								
Tobacco	+	ND	++	++	++	+	++	NA
Carcinogens	++#	ND	ND	ND	+	+#	+	NA
Alcohol	ND	ND	ND	ND	ND	ND	+/-	+/-
Dusts/oils	++	ND	ND	ND	ND	ND	++	NA
Diet								
Vegetables	ND	ND	ND	-	-	ND	--	---
Fruits	ND	ND	ND	-	ND	ND	-	---
Meat	ND	ND	ND	ND	ND	ND	ND	+
Fat	ND	ND	ND	ND	ND	ND	ND	+
Fish	ND	ND	ND	ND	ND	ND	-	+/-

*World Cancer Research Fund,American Institute for Cancer Research 2007; NW, North-West, SW, South-West, S, South; SEM, South-East Mainland; SEI, South-East Island; Pac, Pacific; NE, North-East; L, low; M, medium;, H, high; NA, not applicable; ND, no data; -/--, slight/weak protection, +/-, no effect, +/++/+++, slight, weak, strong risk;# asbestos asnd other fibres for mesotheliomas

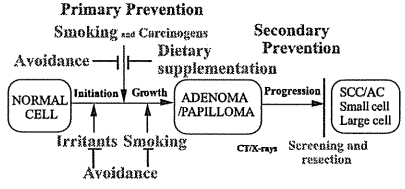

Figure 32. Cancer Prevention and Control Measures for the Lung

the lungs are plotted in Figure 30. The average ratio is almost 0.9:1, with no pronounced exceptions. Males are generally three or four-fold more likely to be affected as females , although there is great variation (see Figure 31). In general, North-East Asian women are more likely to have lung cancer than their North-West counterparts, and South-East more than South-West.

Evidence for risk and protective factors from Asia is summarized in Table 8. The obvious factors which need to be avoided as a preventive measure (see Figure 32) are tobacco and particulate matter that can be breathed in like cooking oils, coal dusts and asbestos, for example. Vegetables and fruits are protective.

Regarding secondary prevention, X-rays for squamous cell carcinoma and spiral computer tomography for adenocarcinoma are in use in some countries, for example in Japan, but these cannot be recommended for general application in Asia.

Urinary Tract

The urinary tract comprises the kidneys, ureter, urinary bladder and associated prostate gland. The cancers in these organs arise from tubular epithelium in the renal case, transitional epithelium where the urine is in contact, and glandular epithelium in the prostate. Since they are linked physically it is conceivable that they might share risk factors to some extent. Comparisons across sites are shown in Figure 33. Generally, incidence rates for kidney cancers

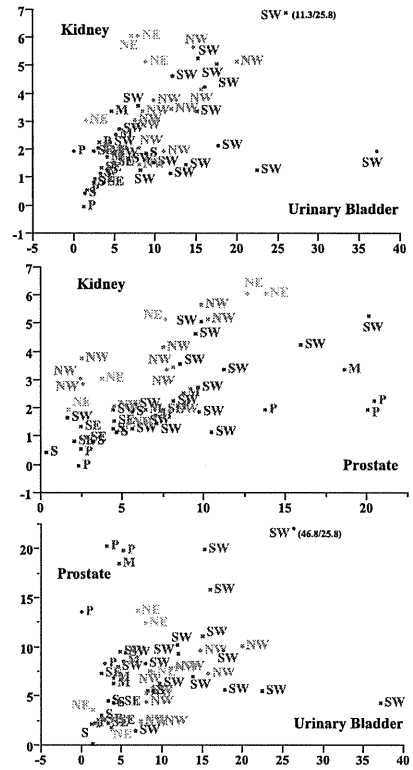

Figure 33. Regional Comparisons Between Globocan Incidence Data for the Sites within the Male Urinary Tract

show a relatively good cross-correlation with data for both urinary bladder and prostate cancers, with notable exceptions of some South-West populations having a bias towards the urinary bladder, and Pacific nations demonstrating high prostate but low kidney rates. North-West Asia tends to have greater incidences of kidney relative to prostate, as compared to neighbouring South-West Asia.

Kidney

The Globocan 2002 mortality/incidence data for the kidney are plotted in Figure 34. The average ratio is 0.65:1, but survival is considerably better in some countries, like Korea and Japan, for example as compared with Kazakhstan in Globocan 2002. Since there is no screening program in place, this presumably reflects clinical treatments. Males are somewhat less than twice as likely as females to be affected, although there is great variation, the ration being apparently almost 1:1 in Bharain but 5:1 in Qatar (see Figure 24).

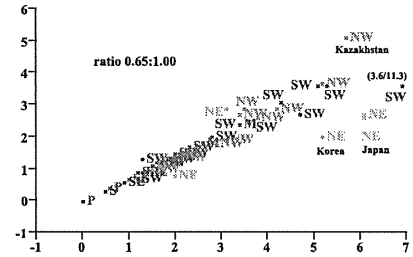

Figure 34. Mortality/Incidence Data for the Kidney
(Globocan 2002; Ferlay et al., 2004)

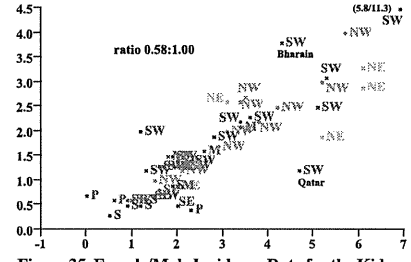

Figure 35. Female/Male Incidence Data for the Kidney
(Globocan 2002; Ferlay et al., 2004)

Table 9. Asian Evidence for Modifying Factors for the Kidney

	NW	SW	S	SEM	SEI	Pac	NE	World*
Prevalence	L	L-M	L	L	L	L-M	L-M	NA
Lifestyle								
Obesity	ND	ND	ND	ND	ND	ND	++	+++
Diet								
Vegetables	ND	ND	ND	ND	ND	ND	--	+/-
Fruits	ND	ND	ND	ND	ND	ND	-	+/-

*World Cancer Research Fund,American Institute for Cancer Research 2007; NW, North-West, SW, South-West, S, South; SEM, South-East Mainland; SEI, South-East Island; Pac, Pacific; NE, North-East; L, low; M, medium;, H, high; NA, not applicable; ND, no data; -/--, slight/weak protection, +/-, no effect, +/++/+++, slight, weak, strong risk

Evidence for risk and protective factors from Asia is summarized in Table 9. The only obvious risk factor is obesity, perhas together with excessive food consumption, while vegetables and fruit are protective. There are no screening measures which could be recommended.

Ureter and Urinary Bladder

The Globocan 2002 mortality/incidence data for the urinary bladder are plotted in Figure 36. The average ratio is 0.65:1, with relatively little variation. Males are generally about five fold more likely to be affected than females, although with very contrasting data for different countries, at least in Globocan 2002 (see Figure 37). Looking at other data for South-West Asia, this needs to be confirmed.

Evidence for risk and protective factors from Asia is summarized in Table 10. The obvious factors which need

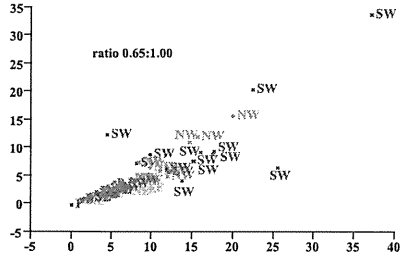

Figure 36. Mortality/Incidence Data for the Urinary Bladder (Globocan 2002; Ferlay et al., 2004)

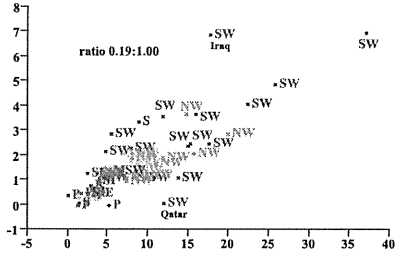

Figure 37. Female/Male Incidence Data for the Urinary Bladder (Globocan 2002; Ferlay et al., 2004)

Table 10. Asian Evidence for Modifying Factors for the Ureter and Urinary Bladder

	NW	SW	S	SEM	SEI	Pac	NE	World*
Prevalence	L-M	L-H	L	L	L	L-M	L	NA
Lifestyle								
Parasites	ND	++	ND	ND	ND	ND	ND	NA
Tobacco	++	++	ND	ND	ND	ND	++	NA
Carcinogens	+	ND	ND	ND	ND	ND	++#	+#
Diet								
Vegetables	ND	ND	ND	ND	ND	ND	--	+/-
Fruits	ND	ND	ND	ND	ND	ND	--	+/-
Meat	ND	ND	ND	ND	ND	ND	+	+/-

*World Cancer Research Fund,American Institute for Cancer Research 2007; NW, North-West, SW, South-West, S, South; SEM, South-East Mainland; SEI, South-East Island; Pac, Pacific; NE, North-East; L, low; M, medium;, H, high; NA, not applicable; ND, no data; -/--, slight/weak protection, +/-, no effect, +/++/+++, slight, weak, strong risk;# arsenic and other environmental carcinogens

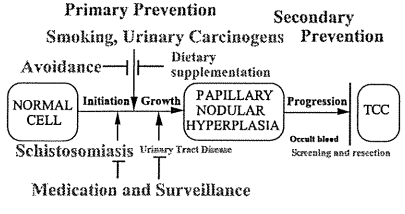

Figure 38. Cancer Prevention and Control Measures for the Urinary Bladder

to be avoided as a preventive measure (see Figure 38) are infestation with Schistosome parasites and tobacco. Other environmetal carcinogens, like arsenic, may also play important roles, while high intake of vegetables and fruits can be recommended, possible because of antioxidant qualities. Meat may be a risk factor.

Regarding secondary prevention, there are no pertinent data, although testing for occult blood is conceivable if a high risk population could be identified.

Prostate

The Globocan 2002 mortality/incidence data for the prostate are plotted in Figure 39. The average ratio is 0.6:1, with the developed countries like Korea and Japan having better survival, for example, than some of the countries

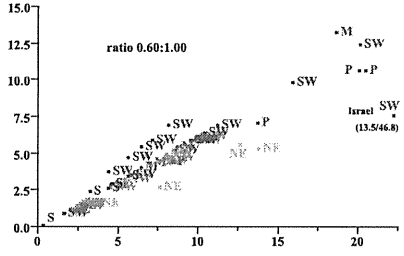

Figure 39. Mortality/Incidence Data for the Prostate (Globocan 2002; Ferlay et al., 2004)

Table 11. Asian Evidence for Modifying Factors for the Prostate

	NW	SW	S	SEM	SEI	Pac	NE	World*
Prevalence	L-M	L-M	L	L	L-M	M-H	L-M	NA
Lifestyle								
Obesity	ND	ND	ND	ND	ND	ND	+	+/-
Exercise	ND	ND	ND	ND	ND	ND	-	+/-
Diet								
Vegetables#	-	ND	ND	ND	ND	ND	--	--
Fruits	ND	ND	ND	ND	ND	ND	-	-
Fat	+	+	ND	ND	ND	ND	+	+/-
Meat	+	+	ND	ND	ND	ND	ND	+/-
Dairy food	ND	+	ND	ND	ND	ND	ND	++
Soy food	ND	ND	ND	ND	ND	ND	---	NA

*World Cancer Research Fund,American Institute for Cancer Research 2007; NW, North-West, SW, South-West, S, South; SEM, South-East Mainland; SEI, South-East Island; Pac, Pacific; NE, North-East; L, low; M, medium;, H, high; NA, not applicable; ND, no data; -/--, slight/weak protection, +/-, no effect, +/++/+++, slight, weak, strong risk; #particular ingredients like lycopene

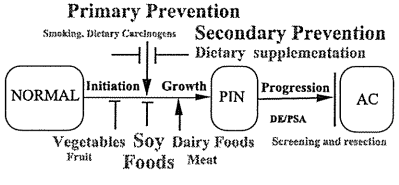

Figure 38. Cancer Prevention and Control Measures for the Prostate

of South-West Asia. The lack of any population-based screening programs in the countries involved would perhaps point to variation in clinical parameters.

Evidence for risk and protective factors from Asia is summarized in Table 11. There are no obvious factors which need to be avoided (see Figure 38), with the possible exception of dairy foods. Regarding prevention, consumption of soy products and vegetables, as well as fruit, would appear to warrant attention.

For secondary prevention, use of prostate specific antigen and digital examination have been examined as possible approaches, but no population-based programs are presently in place anywhere in Asia.

Female Reproductive System

The ovarian, cervical corpus/endometrium and breast constitute the reproductive system, whose cancer development is primarily dependent on hormonal factors. A variety of cancer types arise in the ovary, but in all three sites the adenocarcinoma is prevalent. Cross-site comparisons of incidence data are shown in Figure 39. There is a generally tendency for all three to increase in tandem but there is also interesting regional variation.

For example, North-West Asia clearly demonstrates higher levels of ovarian and particularly endometrial cancer, relative to the breast, than populations in South-West Asia. Within South-East Asia, there are clearly higher levels of all three in the Island and Peninsular countries than in the mainland region.

Ovary, Endometrium and Breast

The Globocan 2002 mortality/incidence data for the three sites are plotted in Figure 40. The average ratios are 0.58:1, 0.58:1 and 0.43:1, respectively, for the ovary, endometrium and breast, in all cases with appreciably better outcomes in the North-East than elsewhere in Asia.

Evidence for risk and protective factors for breast cancer from Asia is summarized in Table 11. The obvious factors which need to be avoided as preventive measure

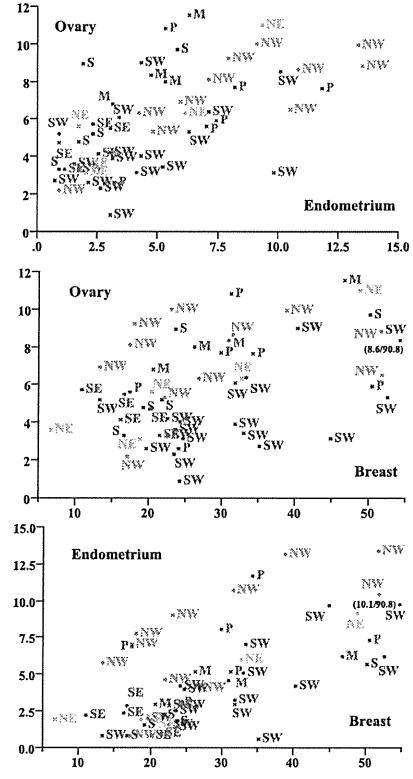

Figure 39. Regional Comparisons Between Globocan Incidence Data for the Various Sites within the Female Reproductive System

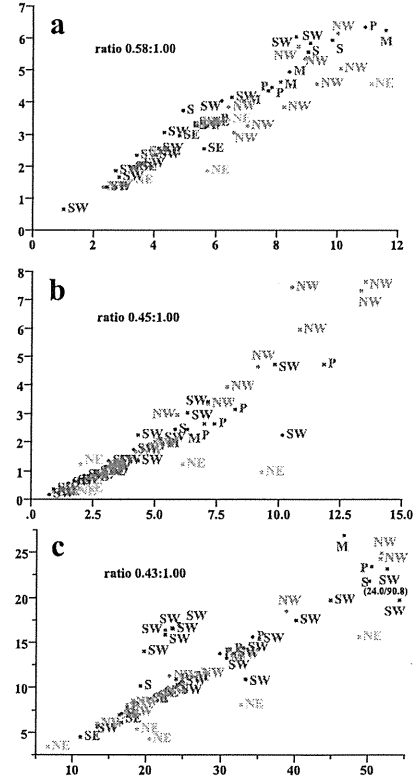

Figure 40. Mortality/Incidence Data for the Ovary (a), Endometrium (b) and Breast (c) (Globocan 2002; Ferlay et al., 2004)

Table 11. Asian Evidence for Modifying Factors for the Breast

	NW	SW	S	SEM	SEI	Pac	NE	World*
Prevalence	L-H	L-M	L-H	L-M	M-H	M-H	L-M	NA
Lifestyle								
Tobacco	+	ND	+	ND	ND	ND	+	NA
Alcohol	ND	ND	ND	+	ND	ND	ND	+++
Obesity	+	++	++	ND	ND	ND	++	++#
Exercise	ND	--	ND	ND	ND	ND	--	--
Reproductive Factors								
Menarche	+	ND	ND	ND	+	ND	++	NA
Menopause	+	ND	ND	ND	+	ND	++	NA
Hormones	ND	+	ND	+/-	+	ND	+	NA
Pregnancy	-	ND	ND	-	ND	ND	--	NA
Lactation	--	--	ND	ND	--	ND	--	---
Diet								
Vegetables#	ND	-	-	ND	-	ND	-	+/-
Fat	ND	+	ND	ND	ND	ND	+	+#
Sugar	ND	+	ND	ND	ND	ND	+	+/-
Fish	ND	ND	ND	ND	ND	ND	--	+/-
Soy food	ND	ND	ND	ND	--	ND	---	NA

*World Cancer Research Fund,American Institute for Cancer Research 2007; NW, North-West, SW, South-West, S, South; SEM, South-East Mainland; SEI, South-East Island; Pac, Pacific; NE, North-East; L, low; M, medium;, H, high; NA, not applicable; ND, no data; -/--, slight/weak protection, +/-, no effect, +/++/+++, slight, weak, strong risk; #postmenopausal

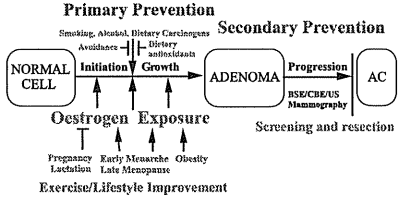

Figure 42. Cancer Prevention and Control Measures for the Breast, Ovary and Endometrium

(see Figure 42) are post-menopausal obesity, early menarche and late menopause, and hormone therapy. Tobacco and alcohol could play minor roles. The strongest protective factors would appear to be exercise, pregnancy, lactation, and consumption of soy products, followed by intake of fish and vegetables.

For the ovary and endometrium, the same factors generally apply, with possibly stronger influence of vegetables, and negative influence of smoking, fat and meat. Lactation may not be important in the endometrium.

Regarding secondary prevention, breast self-examination may be the most effective approach in much of Asia, if only to improve awareness and early presentation at hospital when symptoms are detected. In the developed countries, mammography has proven efficacy. For the ovary and endometrium, no population-based approaches are warranted at present.

Cervix

Since cancer of the uterine cervix has a primarily non-hormonal aetiology, it is here treated separately from the remainder of the female reproductive system. Perhaps the closest site in the body for comparison is the oral cavity, where the human papilloma virus may also be exerting an impact. A comparison of Globocan 2002 incidence data for the two is given in Figure 43. Clearly, some Pacific and South Asian populations do have high rates for both, but there are also a number of exceptions.

The Globocan 2002 mortality/incidence data for the cervix are plotted in Figure 44. The average ratio is 0.53:1, with little variation, except marginally better survival overall in North-West as opposed to South-West Asia.

Evidence for risk and protective factors for uterine cervix cancer from Asia is summarized in Table 12. The

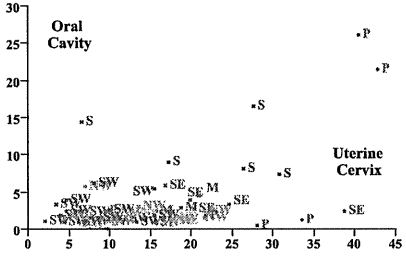

Figure 43. Regional Comparisons Between Globocan Incidence Data for the Cervix and Oral Cavity

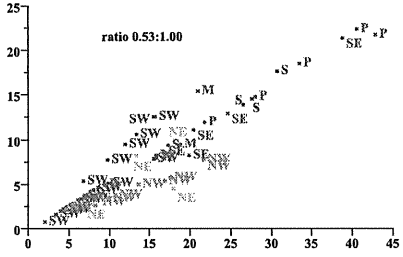

Figure 44. Mortality/Incidence Data for the Uterine Cervix (Globocan 2002; Ferlay et al., 2004)

Table 12. Asian Evidence for Modifying Factors for the Uterine Cervix

	NW	SW	S	SEM	SEI	Pac	NE	World*
Prevalence	L-H	L-M	L-H	M-H	M-H	M-H	L-M	NA
Lifestyle								
HPV	+++	+++	+++	+++	+++	+++	+++	NA
Tobacco	ND	ND	ND	++	++	ND	++	NA
Reproductive Factors								
Pregnancy	ND	ND	ND	+	ND	ND	+	NA
Early Sex	ND	ND	+	ND	ND	ND	+	NA
VD	ND	ND	ND	+	+	ND	++	NA
Diet								
Vegetables	ND	ND	ND	-	ND	ND	ND	-
Fruit	ND	ND	ND	-	ND	ND	-	+/-
Fish	ND	ND	ND	-	ND	ND	-	+/-

*World Cancer Research Fund,American Institute for Cancer Research 2007; NW, North-West, SW, South-West, S, South; SEM, South-East Mainland; SEI, South-East Island; Pac, Pacific; NE, North-East; L, low; M, medium;, H, high; NA, not applicable; ND, no data; -/--, slight/weak protection, +/-, no effect, +/++/+++, slight, weak, strong risk

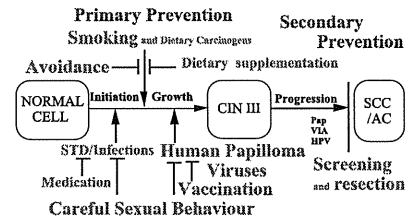

Figure 45. Cancer Prevention and Control Measures for the Uterine Cervix

obvious factors which need to be avoided as preventive measures are infection with high risk human papilloma viruses and smoking, and to a lesser extent sexually transmitted disease (see Figure 45). Dietary factors appear marginal. The main approaches should therefore be vaccination, where this is financially conceivable, and screening and resection using the Pap smear, visual inspection or HPV testing methods. The actual approach adopted will naturally be dependent on physical and financial constraints.

Nervous and Endocrine

Brain and Nervous Tissue

The Globocan 2002 mortality/incidence data for the brain and nervous tissue are plotted in Figure 46. The average ratio is 0.8:1, with little variation except for the slightly better survival evident for North-East Asian

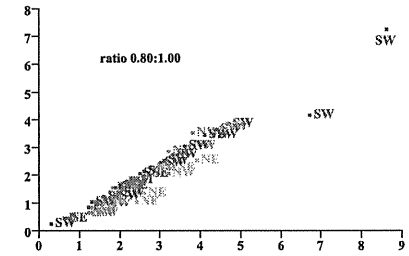

Figure 46. Mortality/Incidence Data for the Brain and Nervous Tissue (Globocan 2002; Ferlay et al., 2004)

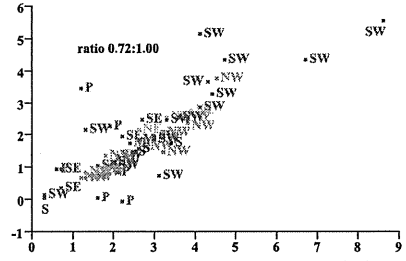

Figure 47. Female/Male Incidence Data for the Brain and Nervous Tissue (Globocan 2002; Ferlay et al., 2004)

populations. Males are somewhat more likely than females to be affected (see Figure 47). Research data for risk factors are limited but certain environmental chemicals, cell phone use, salt and liquor may play roles, while vegetables and fruit are protective.

Thyroid

Since women are generally more susceptible to development of thyroid cancer than males, there may be some sex hormone involvement. In fact there is a very general correlation between thyroid and breast cancer incidences across Asia. As shown in Figure 48, that is also to some extent true for the endometrium, but South-West and North-West populations clearly differ in the relative percentages of cancers in the two sites.

The relevant Globocan 2002 mortality/incidence data are plotted in Figure 49, the average ratio of 0.32:1 having a few exceptions. There is a massive more than three fold

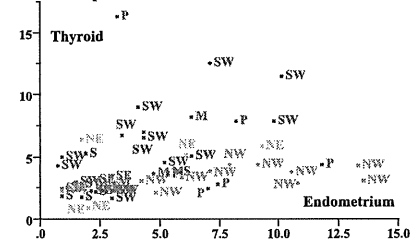

Figure 48. Regional Comparisons Between Globocan Incidence Data for the Throid and Endometrium

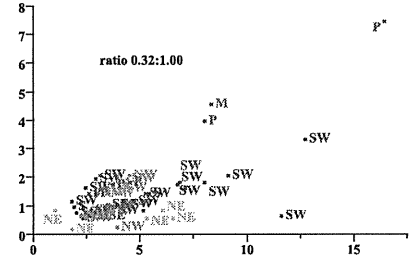

Figure 49. Mortality/Incidence Data for the Thyroid (Globocan 2002; Ferlay et al., 2004)

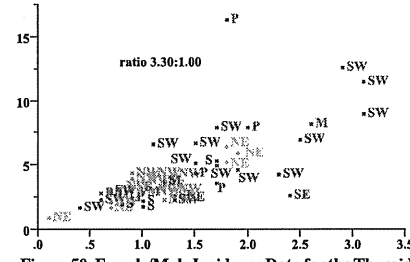

Figure 50. Female/Male Incidence Data for the Thyroid (Globocan 2002; Ferlay et al., 2004)

female predominance (see Figure 50), rising to over seven fold in Vanuatu. Radiation, reproductive parameters, obesity and conditions causing goiter are the best established risk factors but more research needs to be focused on the marked geographical variation.

Hematopoietic System

Globocan incidence data for non-Hodgkins lymphomas and leukemias ares plotted in Fibure 48, a general correlation between the two being apparent. There are marked regional groups, with a cluster of South-West Asian populations demonstrating the highest values.

Non-Hodgkins Lymphoma (NHL)

The Globocan 2002 mortality/incidence data for NHL

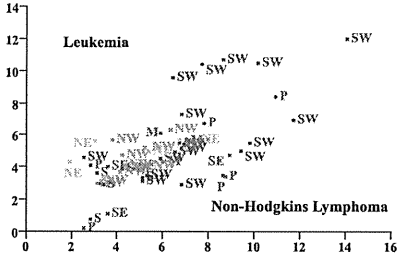

Figure 48. Regional Comparisons Between Globocan Incidence Data for the Throid and Endometrium

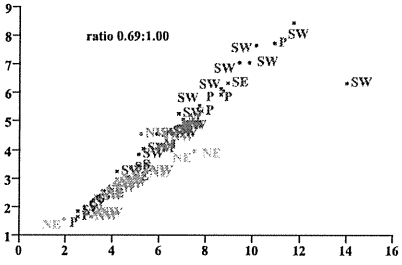

Figure 51. Mortality/Incidence Data for Non-Hodgkins Lymphomas (Globocan 2002; Ferlay et al., 2004)

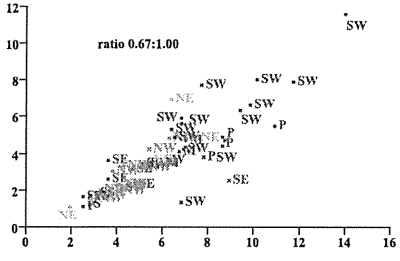

Figure 52. Female/Male Incidence Data for Non-Hodgkins Lymphomas (Globocan 2002; Ferlay et al., 2004)

are plotted in Figure 49. The average ratio is 0.69:1, with very little marked variation except for the better outcome in Israel among the high incidence populations. The gender differential is in the direction of males, but the extent is slight, in line with radiation as the major risk factor. Other etiological agents may be viruses, like HBV, and exogenous environmental carcinogens.

Leukemia

The Globocan 2002 mortality/incidence data for leukemias are plotted in Figure 53. The average ratio is 0.82:1, again with Israel having a pronouncedly better survival. The slight male predominance is also in line with radiation and environmental pollution as the major risk factors.

Conclusions

From the present survey we can conclude that, for many of the cancers, epidemiological data on risk factors are limited in some regions of the Asian Pacific. This certainly does not mean that no recommendations can be made with regard to preventive measures. Indeed, the findings extracted from the series of seven regional reviews included in this volume (Long et al., 2010; Moore et al., 2010a; 2010b; 2010c; 2010d; 2010e; Salim et al., 2010) are well in agreement with the massive body of results for the entire globe reviewed by the World Cancer Research Fund/American Institute for Cancer Research for its summary document (2007). However, we are just as certainly lacking in a firm understanding of the reasons

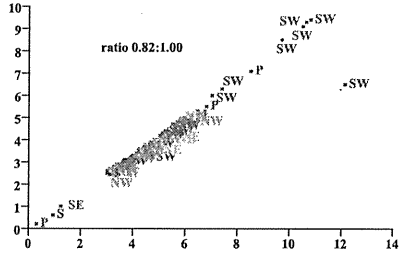

Figure 53. Mortality/Incidence Data for Leukemias (Globocan 2002; Ferlay et al., 2004)

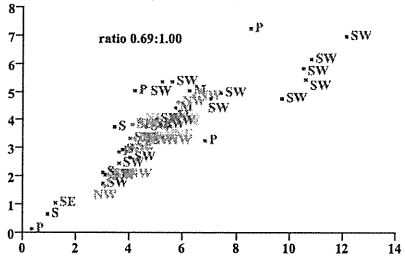

Figure 54. Female/Male Incidence Data for Non-Hodgkins Lymphomas (Globocan 2002; Ferlay et al., 2004)

for the, in many cases, marked geographical and gender dependence. The hope is that collaborative research in the Asian Pacific can make a major contribution to generating that understanding.

Of necessity, recourse was here made to Globocan 2002 data, the only database in the public domain which is comprehensive. Clearly, the included information is not up to date and Globocan 2007, now under construction, is keenly awaited. For many of the countries included we must take account of the fact that the estimates may be inaccurate, given the paucity of the information available for their calculation. Examples where mortality exceed the incidence are difficult, although not impossible to explain (with rapid change in incidence over time for example). Nevertheless, a general picture can be painted. That was the aim of the present strategies document - to provide a framework for many questions to be asked and hopefully provide some directions in which they might be answered with contributions from interested researchers across the region.

The authors invite critical comments and hope that all scientists active in cancer control will join the research consortia which will be established and given opportunities to meet and continuously interact for positive discourse at the twin Asian Pacific major assemblies, the Asian Pacific Cancer Congresses and the Asian Pacific Organization for Cancer Prevention (and Control) General Assembly Conferences and other events with similar goals in the future.

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REGIONAL REVIEW

Cancer Epidemiology and Control in North-East Asia - Past, Present and Future

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Abstract

China, Mongolia, Korea and Japan constitute North-East Asia. For reasons of largely shared ethnicity and culture, with various degress of mixed Chinese and Altaic elements, as well as geographical contiguity, they can be usefully grouped together for studies of chronic disease prevalence and particularly cancer. The fact of problems shared in common, with increasing disease rates, underlines the necessity for a coordinated approach to research and development of control measures. To provide a knowledge base, the present review of cancer registration and epidemiology data was conducted. The most frequent cancers in males of North-East Asia are in the lung, liver and stomach, with considerable geographical and temporal variation in their respective prevalences. However, colorectal cancer is also of increasing importance. In females the breast, together with the lung in China, the liver in Mongolia and the stomach in Korea and Japan, are most frequent. Variation in risk factors depends to a large extent on the local level of economic development but overall the countries of the region face similar challenges in achieving effective cancer control.

Asian Pacific J Cancer Prev, **10**, 107-148

Introduction

China, Mongolia, Korea and Japan constitute North-East Asia with a population in excess of 1,700 million. They share a great deal in terms of culture and this is reflected to some extent in the prevalent types of non-communicable disease, including cancer. Naturally, they also present socioeconomic diversity and this allows pointers to be gained into etiological factors. The present review concerns cancer registration findings, available at the International Agency for Cancer Research Descriptive Epidemiology group website (www-dep.iarc.fr), and published information on epidemiology of the disease, accessible through PubMed.

Cancer Registration in North-East Asia

The population-based cancer registries included in Cancer Incidence in Five Continents (CI5) are listed in Table 1 and members of the International Association for Cancer Registries within the region are shown in Figure 1. Since there a national registry only exists for Korea, data from Globocan 2002 have been used for comparison purposes to generate percentages of all cancers accounted for by the five most frequent tumours, shown in Figure 2.

In China, a national survey of cancer mortality for the period of 1973-1975 was organized by the Chinese Ministry of Public Health hospitals and cancer institutes were established nationwide (Wang, 2001). The Shanghai and Hong Kong Cancer Registries were established in the 1960's, and have been reporting to CI5 since Vol IV (Foo et al., 2001). The Taiwan Cancer Registry was founded in

Table 1. Numbers of North-East Asian Registries in the Series of Nine Volumes of CIV

Volume	I	II	III	IV	V	VI	VII	VIII	IX
Chinese									
Beijing/Changle/Cixian/Taiwan/Wuhan								1	
Guangzhou/Nangang District, Harbin									1
Hong Kong				1	1	1	1	1	1
Jiashan								1	1
Qidong						1	1	1	
Shanghai				1	1	1	1	1	1
Tianjin					1	1	1	1	
Koreans									
Busan/Daegu/Seoul								1	1
Daejeon/Gwangju/Inchon/Ulsan/Jejudo									1
Kangwa							1	1	
Japanese									
Aichi/Fukui									1
Hiroshima					1	1	1	1	1
Miyagi	1	1	1	1	1	1	1	1	1
Nagasaki				1	1	1	1	1	
Osaka			1	1	1	1	1	1	1
Saga						1	1	1	
Yamagata						1	1	1	1

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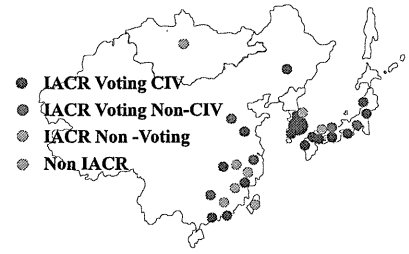

Figure 1. Cancer Registries in North-East Asia

1979 (You et al., 2001). Now a total of six registries are reporting to CI5 and there are 13 Voting and 10 non-Voting Chinese members of IACR. First data for Shanghai were published by Jin et al (1993) and subsequently cancer incidences across the country (Yang et al., 2005) and for Shanghai (Jin et al., 1999), Qidong (Chen et al., 2006; 2007), Guangzhou (Cao et al., 2008) and Tianjin (Song et al., 2008) have appeared. Mortality in Beijing was the subject of another report (Wang et al., 1995).

In 1971, cancer registration was introduced on a national basis in Mongolia, using a system modeled upon that developed in the Soviet Union and featuring notification of all newly diagnosed cancer cases by oncology clinics located in the provincial hospitals (Munkhtaivan et al., 2001). There are no data published in peer-review journals and there is no IACR member.

Cancer registration was started in Korea in 1980 with financial support of the World Health Organization (Ahn, 2001). Subsequently, the Ministry of Health and Welfare compelled all the university and training hospitals to join the Korean Central cancer Registry program. Now there is a very comprehensive nationwide program (Ahn, 2007; Shin 2008), with nine registries reporting to CI5 and 10 IACR members, 8 Voting and 2 Associate. First population-based data were published in 1995 (Kim et al., 1995) and nationwide incidence rates for 1999-2001 were first published in 2005 (Shin et al, 2005). Research data are available for trends in incidence (Chung et al, 2007; Jo et al, 2007; Shin et al., 2008), survival rates (Lee et al, 2007; Jung et al., 2007; Yang and Bae, 2007; Kim et al., 2008) and influence of income (Kim et al., 2008).

In Japan, the first survey of cancer incidence, in Miyagi prefecture, was conducted in 1951-1953 by Segi and his colleagues. Population-based cancer registries were first

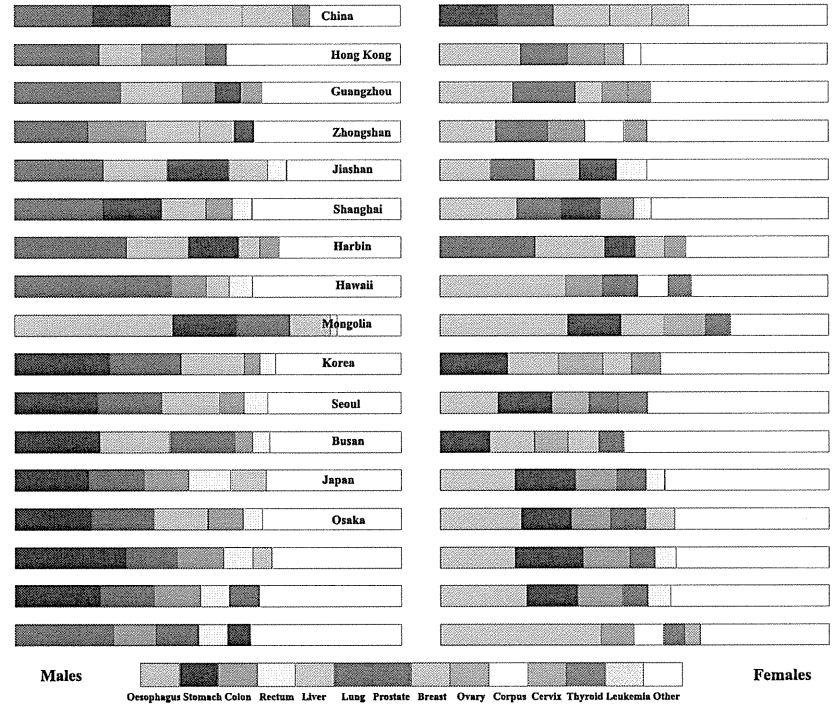

Figure 2. Percentage Data for the Five Most Prevalent Cancers in Populations of North-East Asia. Country data are from Globocan 2002 and individual registry data from Curado et al., 2007

Table 2. Population-based Cancer Incidences/100,000 for North-East Asians - Males*

	Chinese							Korea		Japan			
	HK#	Zhong	Jiashang	Shanghai	Harbin	Taiwan	Hawaii	Seoul	Pusan	Osaka	Yama	Miyagi	Hawaii
Lip	0.1	0.1	0.1	0.6	0.1	0.7	0.1	0.1	0.0	0.0	0.1	0.1	0.0
Tongue	1.7	1.9	0.6	0.6	0.5	5.1	2.2	1.0	1.0	1.6	1.5	1.5	3.0
Mouth	1.6	1.3	0.6	0.8	0.4	9.3	1.5	1.4	1.3	1.4	1.2	1.3	1.2
Nasopharynx	17.8	26.9	4.0	4.1	1.3	13.6	9.9	1.1	0.8	0.5	0.4	0.5	0.6
Hypopharynx	1.4	0.8	0.5	0.2	0.3	-	2.1	1.2	1.0	1.5	1.1	1.4	1.7
Oesophagus	9.5	16.5	20.2	9.2	10.3	7.9	5.4	7.1	8.1	10.8	13.0	15.4	6.0
Stomach	14.7	9.4	32.1	34.1	24.8	18.6	4.6	63.7	59.9	51.3	79.4	65.8	17.2
Colon	23.8	8.5	9.8	15.8	9.4	15.1	21.6	18.7	12.7	23.6	33.9	36.0	31.9
Rectum	7.0	8.7	10.7	11.2	8.6	13.7	11.4	17.4	12.6	13.5	21.7	22.4	21.8
Liver	29.5	25.7	33.8	25.9	30.3	51.9	13.9	44.1	49.8	35.6	14.3	16.4	8.5
Gallbladder	2.9	4.4	2.2	3.2	2.1	2.6	1.2	8.0	9.3	5.7	8.4	6.9	2.4
Pancreas	4.5	2.6	7.1	7.5	7.5	4.7	8.2	8.7	7.7	9.3	9.9	10.1	7.8
Larynx	4.4	5.1	1.1	2.8	3.8	3.5	3.1	4.7	4.9	2.4	2.9	3.3	3.2
Trachea, lung	57.9	34.0	46.7	51.5	55.5	38.2	28.6	49.7	46.2	43.3	38.2	40.6	31.0
Penis	0.2	0.6	0.9	0.3	0.3	0.5	0.0	0.2	0.2	0.1	0.2	0.3	0.2
Prostate	15.0	2.2	1.4	6.9	2.1	11.9	69.1	12.7	7.3	11.3	13.4	22.0	74.2
Kidney	3.3	1.8	1.6	4.8	3.2	5.7	6.2	5.6	4.9	3.9	3.4	6.6	8.4
Bladder	10.9	5.0	5.9	8.1	6.2	8.9	7.5	11.0	10.2	7.9	7.4	10.6	13.0
Brain	3.4	1.9	4.0	5.7	5.6	3.8	1.7	3.5	3.0	2.5	2.4	2.7	3.2
Thyroid	2.2	0.9	1.0	1.4	0.7	1.5	1.6	2.5	2.2	1.3	1.5	2.0	1.8
Non-Hodgkin	8.1	4.3	3.4	5.5	3.1	5.8	13.9	6.8	4.5	6.2	5.7	7.4	11.1
Leukemia	5.5	4.8	3.1	3.6	2.7	4.9	5.9	5.2	4.6	5.7	4.0	4.9	8.7
Total	265	181	205	226	194	250	239	298	274	256	281	302	286

*Data from Curado et al, 2007, except for Taiwan, Parkin et al., 2002; #Hong Kong; Zhong, Zhongshan; Yama, Yamagata

Table 3. Population-based Cancer Incidnece/100,000 Data for North-East Asians - Females*

	China							Korea		Japan			
	HK#	Zhong	Jiashang	Shanghai	Harbin	Taiwan	Hawaii	Seoul	Pusan	Osaka	Yama	Miyagi	Hawaii
Lip	0.1	0.1	0.0	0.0	0.1	0.1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
Tongue	1.0	0.6	0.2	0.5	0.2	0.9	1.2	0.5	0.4	0.7	0.7	0.8	1.2
Mouth	0.7	0.4	0.1	0.6	0.4	1.1	0.3	0.6	0.5	0.7	0.4	0.6	0.5
Nasopharynx	6.7	10.1	1.3	1.5	0.5	3.6	1.1	0.3	0.3	0.1	0.1	0.1	0.2
Hypopharynx	0.1	0.0	0.2	0.0	0.0	-	0.0	0.1	0.1	0.1	0.3	0.2	0.0
Oesophagus	1.7	1.9	4.8	3.0	1.7	0.8	0.0	0.6	0.7	1.7	1.6	2.2	0.7
Stomach	7.3	4.2	10.6	17.2	11.6	10.9	4.1	27.1	23.9	19.8	31.3	24.2	7.2
Colon	18.9	6.5	8.7	14.6	7.8	12.9	17.3	11.5	7.8	15.0	21.1	21.5	22.0
Rectum	4.2	6.0	9.2	8.3	6.8	10.6	4.8	9.7	7.4	6.5	10.2	10.9	9.8
Liver	7.3	5.0	12.6	8.3	10.3	19.4	3.9	13.0	14.9	11.2	5.9	5.6	3.5
Gallbladder	2.8	2.4	3.4	5.1	2.0	2.7	1.3	6.3	7.4	4.7	6.0	5.2	1.5
Pancreas	3.1	1.4	5.4	5.3	5.1	3.5	5.0	5.0	3.8	5.4	5.1	6.3	8.3
Larynx	0.3	0.3	0.2	0.2	0.7	0.3	0.1	0.4	0.6	0.2	0.1	0.2	0.4
Trachea, lung	23.4	14.8	13.0	19.9	34.6	17.9	16.7	14.4	12.2	13.9	11.7	12.5	13.7
Breast	41.3	15.4	14.7	35.2	25.7	31.3	59.5	28.8	21.2	32.0	35.3	42.5	107.5
Ovary	2.9	4.1	3.7	7.1	5.2	5.7	5.6	5.9	5.1	5.3	6.2	7.0	10.3
Corpus uteri	8.8	10.8	1.0	6.0	2.8	4.3	13.1	3.5	2.4	3.3	5.5	5.9	19.6
Cervix uteri	9.8	3.5	2.4	2.8	3.0	24.9	4.7	17.8	15.3	5.6	6.8	6.0	5.2
Kidney	1.7	0.6	0.6	2.4	1.9	4.9	2.3	2.2	2.1	1.5	1.9	2.5	3.5
Bladder	2.8	0.9	1.0	2.0	1.8	4.2	1.7	2.1	1.7	1.7	2.0	2.6	2.3
Brain	2.2	1.5	3.6	6.2	4.7	2.8	1.9	3.0	2.1	2.0	1.8	1.8	3.2
Thyroid	7.2	3.0	1.5	4.7	1.2	6.1	11.7	14.1	8.5	3.2	8.0	9.2	6.8
Non-Hodgkin	5.3	2.5	1.6	3.5	1.9	4.5	7.5	4.2	3.2	3.8	3.7	5.2	7.6
Leukemia	4.1	3.3	2.4	3.5	1.5	3.9	4.0	3.8	2.8	3.3	2.9	3.4	6.3
Total	196	108	175	141	105	195	182	191	183	152	179	189	256

*Data from Curado et al, 2007, except for Taiwan, Parkin et al., 2002; #Hong Kong; Zhong, Zhongshan; Yama, Yamagata

established in Hiroshima city in 1957 and in Nagasaki city in 1958 for studying the long-term effects of atomic bomb radiation. In 1959 the Miyagi Tumor Registry was started and cancer registration schemes as part of prefectural

cancer control programs were first provided in 1962 by the Health Departments of Aichi Prefecture and of Osaka Prefecture. Subsequently, this type of cancer registry has gradually spread throughout in Japan (Oshima et al., 2001). Japanese registries have been reporting to CI5 since the inception and there are now data from 7 included. Japan has 10 Voting and 3 non-Voting members of IACR.

In 1975, the Research Group for Population-based Cancer Registration in Japan was organized (Research Group for Population-based Cancer Registration in Japan, 2000) and as of 2007, there were population-based cancer registries in 35 of Japan's 47 prefectures and in one city. The Japanese Association of Cancer Registries (JACR) was organized in 1992 (Okamoto, 2008). To improve completeness of incidence data in Japan, establishment of hospital-based cancer registries at designated cancer-care hospitals across the country is now underway (Sobue, 2008).

The first population-based data were published in 1979 (Fujimoto et al., 1979). Cancer incidences have been detailed for the country (Tsukuma et al., 2005; Tabata et al., 2008) and for individual registries, like Aichi (Ito et al., 2004) and Miyagi (Nishino et al., 2004). Papers have appeared on variability in cancer incidence rates across registries (Murata et al., 2008; Moore et al., 2005b), data quality (Ajiki et al., 1998; Mori et al., 2005), projected cancer prevalence (Tabata et al., 2008) and mortality and survival (Kaneko et al., 2003; Nomura et al., 2006). Cancer data for Hiroshima and Nagasaki atomic bomb survivors have also been reported (Mabuchi et al., 1994).

There is considerable variation in the most important cancers among registries within North-East Asia (see Figure 2). For a glimpse of the possible future, data for Hawaiin Chinese and Japanese populations are also included. Given the evident trends, the adenocarcinomas will continue to increase, with a major increment in prostate and breast cancer, while the relative importance of lung, stomach and liver should become reduced. Population-based data are summarized in Tables 2 and 3.

Organ Specific Epidemiology

Skin Cancer

Melanoma incidences are very low across the region. There is also a sparcity of literature, basically limited to the link with arsenicosis in Taiwan (Ling and Liao, 2007) and inorganic arsenic in cooked hikiji in Japan (Nakamura et al., 2008), a report of very slight increase in melanoma incidences in Japanese females in the past (Tanaka et al., 1999), sun as a risk factor even in the non-sensitive Japanese (Araki et al., 1999), and increasing risk of eyelid basal cell carcinoma in Taiwan (Lin et al., 2006).

Oral Cancer

Cancer of the oral cavity is relatively rare in most of the region (see Figure 3), with little variation over time, although the islands of Taiwan and Hainan are clear exceptions because of the prevalence of betel chewing (Ho et al., 2002; Lin et al., 2005). Tobacco might also be playing a role and synergistic effects of variant genotypes of DNA repair enzymes with smoking have been noted in Taiwan (Bau et al., 2007). Betel quid chewing habits, however, seem to carry differing risk between geographic areas, since both Hainan and Hunan have high incidence of chewers while lesions are much more prevalent in the former (Zhang and Reichart, 2007). The Epstein-Barr virus appears to be a risk factor for oral cancer in Okinawa (Higa et al., 2002). Generally the risk factors are carcinogenic effects of cigarette smoking and alcohol (Ide et al., 2008). Coffee consumption has been associated with a lowered risk (Naganuma et al., 2008) but no clear inverse association with green tea consumption was observed in another relatively recent study (Ide et al., 2007).

Given the relatively low prevalence rates, there has been little interest in screening, although a satisfactory participation rate could be obtained in Japan for oral mucosal screening when this was coupled with a general health screen conducted at the same visit (Nagao et al., 2000).

Oesophageal Cancer

Oesophageal cancer is very prevalent in China and Mongolia, with relatively high levels also found in Korea and Japan (see Figure 4). Females have very much lower rates than males. There has been a striking decrease in oesophageal cancer over the past decades in Chinese populations (Ke, 2002), but not in Japan (see Figure 5). In Cixian, mountainous areas have shown a declining trend in incidence while in the plain areas it remained steady, but in both cases mortality rate demonstrated a significant

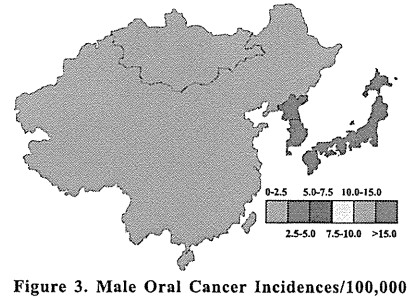

Figure 3. Male Oral Cancer Incidences/100,000 (Globocan, 2002: Ferlay et al., 2004)

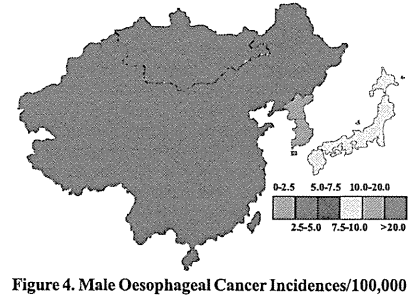

Figure 4. Male Oesophageal Cancer Incidences/100,000 (Globocan, 2002: Ferlay et al., 2004)

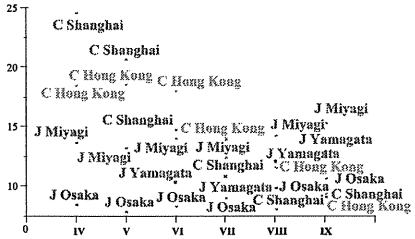

Figure 5. Oesophageal Cancer Incidences/100,000 over Time (Waterhouse et al., 1982; Muir et al., 1987; Parkin et al., 1992; 1997; 2002; Curado et al., 2007)

decrease from 1969 to 2002 (He et al., 2006). Mortality has also decreased in Linzhou (Sun et al., 2007). The steady decrease in Hong Kong observed for both males and females was in line with the increased intakes of fresh vegetables and decreased alcohol drinking, tobacco smoking, and preserved food consumption observed in the population (Tse et al., 2007). Esophageal adenocarcinoma also declined among both males and females, even more than for esophageal squamous cell carcinoma, so that the relative ratio decreased (Yee et al., 2007).

While the vast majority of esophageal cancers in the region are of squamous type (SCC), the adenocarcinoma (AC) accounts for up to 10%, with a slightly greater proportions in females than in males in most registries (see Table 4).

The two most important etiological factors in North-East Asia appear to be alcohol and smoking (Tran et al., 2005; Liu et al., 2006; Wang et al., 2007; Fan et al., 2008), as evidenced also by combined effects with relevant polymorphisms, for example the GSTM1 null genotype with tobacco use (Gao et al., 2002; Lu et al., 2006) and

Table 4. Oesophageal Cancer Histopathology: SCC-AC Percentages

	Male			Female		
	SCC	AC	Ratio	SCC	AC	Ratio
Guangzhou	84.1	3.6	23.4:1	82.4	1.2	68.7:1
Hong Kong	89.1	5.0	17.8:1	83.2	6.8	12.2:1
Jiashan	93.4	6.1	15.3:1	91.5	6.8	13.4:1
Shanghai	18.7	1.7	11.0:1	16.9	2.0	8.4:1
Zhongshan	73.4	2.8	26.2:1	73.7	5.3	13.9:1
Busan	93.5	2.9	32.2:1	72.9	5.0	14.6:1
Daegu	89.5	4.7	19.0:1	83.2	6.8	12.2:1
Daejeon	90.3	2.4	37.6:1	83.2	6.8	12.2:1
Gwangju	91.2	3.2	28.5:1	83.2	6.8	12.2:1
Incheon	89.4	5.1	17.6:1	83.2	6.8	12.2:1
Jejudo	90.0	2.5	36.0:1	72.9	5.0	14.6:1
Seoul	92.7	3.4	27.3:1	85.6	14.6	5.9:1
Ulsan	91.2	7.4	12.3:1	72.9	5.0	14.6:1
Aichi	88.4	6.8	13.0:1	87.5	8.3	10.5:1
Fukui	92.3	2.3	40.0:1	86.0	6.0	14.3:1
Hiroshima	94.8	1.7	55.8:1	93.9	2.0	47.0:1
Miyagi	91.3	3.2	28.5:1	91.2	1.9	48.0:1
Nagasaki	93.1	2.3	40.5:1	93.3	1.9	49.0:1
Osaka	88.4	4.1	21.6:1	86.7	3.9	22.2:1
Yamagata	90.7	4.9	18.5:1	86.0	10.5	8.2:1

*Incidence data from Curado et al., 2007

ADH/ALDH and MTHFR polymorphisms with ethanol exposure (Gao et al., 2004b; Cai et al., 2006; Jiang et al., 2006; Yang et al., 2007; Guo et al., 2008b). In smokers there may be links with ALDH2*1/*2 (Yokoyama et al., 2006) and thymidylate kinase (Gao et al., 2004a). A role for DNA repair has been suggested and the XPA23 polymorphism may be a useful marker for identifying susceptible individuals (Guo et al., 2008). Genetic variants in TGFB1 and TGFBR2 may modulate the risk (Jin et al., 2008). Geographic variation of the associations between smoking, alcohol drinking and risk may exist, despite a similar prevalence of these risk factors (Wu et al., 2006).

This is presumably linked to other risk factors for esophageal SCCs, including poverty and drinking water other than from a tap, and extremes of salt intake in China (Xibin et al., 2003). Diet or well water may be contaminated with nitrosamines (Lin et al., 2002; Zhang et al., 2003). In fact, high-risk areas of EC in China are mostly drought-prone, relatively low altitude areas (Wu and Li, 2007; Wu et al., 2008). Consuming acrid food, fatty meat, moldy food, salted and pickled vegetables, eating fast, introverted personality, passive smoking, a family history of cancer, esophageal lesion, and infection with *Helicobacter pylori* were all found to be significant risk factors in Huaia (Wang et al., 2006). Salted fish, particularly together with smoking, may further contribute (Ke et al., 2002).

Increased consumption of vegetables, fruits, seafood, tea and milk were found to be protective against the development of esophageal cancer (Takezaki et al., 2001; Gao et al., 2002; Fan et al., 2008). Frequent vegetable and garlic consumption appears to contribute to low mortality rates for esophageal and stomach cancers in a low-epidemic area, counteracting similar exposure levels of risk factors like pickled vegetables salty fish, leftover grueland broiled meat as in the high-epidemic area (Takezaki et al., 2003). Green tea drinking protects in women (Wang et al., 2007). So does a high body mass index (BMI), while demonstrating a positive association with adenocarcinoma (Smith et al., 2008). Higher serum 25(OH)D concentrations were associated with significantly increased risk of ESCC in men (Chen et al., 2008a). Hiatal hernia, linked to body size, in combination with other reflux conditions and symptoms, is associated strongly with the risk of esophageal adenocarcinoma (Wu et al 2003).

A number of studies have focused on possible links with HPV, infection being high in esophageal carcinomas of Henan emigrants, local residents and patients in Hubei Cancer Hospital (Yao et al., 2006). Viruses were also found in 30% of Kazakh esophageal cancer patients (Lu et al., 2008) and in 65% of cases in Gansu, where the incidence is high, as compared to 6% in Shandong, a low incidence area, although copy number was also low (Shuyama et al., 2007). However, studies in Linxian, China, did not provide support for a major role of HPV 16, HPV 18 and HPV 73 in the etiology of esophageal cancers (Guo et al., 2006; Kamangar et al., 2006).

Health risk appraisal models may provide an important approach to early intervention strategies to control esophageal SCC in Japanese men (Yokoyama et al., 2008)

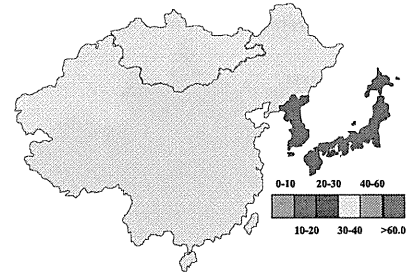

Figure 6. Male Stomach Cancer Incidences/100,000 (Globocan, 2002: Ferlay et al., 2004)

Flushing in response to alcohol may be used in large-scale epidemiological studies as a surrogate marker of ALDH2 genotype to predict individual cancer risk (Yokoyama et al., 2003). While a mechanical balloon for detection of oesophageal cancer in high risk areas has long been advocated, the accuracy is too low for a primary screening test (Pan et al., 2008).

Stomach Cancer

Stomach cancer continues to be a major problem in Japan and Korea, with relatively high incidences also in China (as in Jiashang and Shanghai) and Mongolia (see Figure 6). Gradual decrease has been observed in some registries (see Figure 7) with a declining trend for mortality from gastric cancer in Linzhou (Sun et al., 2007) and both incidence and mortality in Zhaoyuan County (Wang et al., 2007) and Changle (Tian and Chen, 2006). Mortality and incidence ratios have also demonstrated downward trends in Tianjin (Dai et al., 2008; Song et al., 2008).

For risk factor assessment it is clearly important to take into account the site within the stomach. Thus different factors appearing to impact to different extents in the cardia and antrum (Inoue et al., 1999; 2000; 2002; Sasazuki et al., 2002). *Helicobacter pylori* influence is generally considered greatest in the antrum (Machida-Montani et al., 2004), where atrophic changes occur (Tatemichi et al., 2008). With the bacteria it is the cagA-positive strains causing gastritis that are most important (Nobuta et al., 2004; Gwack et al., 2006). Korean and Japanese gastritis

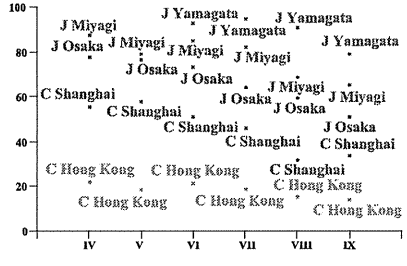

Figure 7. Gastric Cancer Incidences/100,000 over Time (Globocan, 2002) (Waterhouse et al., 1982; Muir et al., 1987; Parkin et al., 1992; 1997; 2002; Curado et al., 2007)

is reported to be characterized by more male- and antrum-predominant acute foveolitis (Lee et al., 2005). Major contributions for inflammation are furhter evidenced by findings for polymorphisms in interleukin genes (Lu et al., 2005;Wu et al., 2008). A close relationship between *H. pylori* infection and intestinal metaplasia and gastric cancer has been hypothesized(Kim et al., 2008)

Other factors include high dietary salt intake, for example from Miso soup (Machida-Montani et al., 2004), fish sauce (Cai et al., 2000) or Kimchi and soybean pastes (Nan et al., 2005), which may interact with *Helicobacter pylori* infection (Kurosawa et al., 2006; Shikata et al., 2006). Distinct increase as the nitrate:antioxidant vitamin consumption ratio increases may be related to this (Kim et al., 2007). The reason why a western-style breakfast protected in one study in Japan (Tokui et al., 2005) but not in another (Masaki et al., 2003) might be linked with relative salt intake.

Cigarette smoking is also associated with increased risk (Huang et al., 2004; Fujino et al., 2005; You et al., 2005; Yun et al., 2005; Nishino et al., 2006; Kim et al., 2007; Shikata et al., 2008). It has been argued that the observed sex dependence may be due to tobacco (Sasazuki et al., 2008). Both differentiated and non-differentiated histologic subtypes were affected in one study (Koizumi et al., 2004), but only the differentiated type of distal gastric cancer (Sasazuki et al., 2002) or the diffuse-type (Suzuki et al., 2007) in others. However, in China it was reported that cardia and upper-third gastric cancers are more strongly related to smoking status than distal gastric cancer (Sung et al., 2007). A link with carcinogen exposure is in line with findings for polymorphisms of DNA repair enzymes (Dong et al., 2008).

Epidemiologic evidence for an association between alcohol drinking and gastric cancer risk in Japan has been concluded to be insufficient due to the methodological quality of studies (Shimazu et al., 2008). However, strong associations with MTHFD variants have been documented (Shen et al., 2005; Wang et al., 2007) and folate may be protective (Weng et al., 2006). Genetic polymorphisms of the E-cadherin promoter also play a role in China (Zhang et al. 2008), as do CYP2E1, GSTT1, GSTP1, GSTM1, ALDH2, and ornithine decarboxylase (You et al., 2005).

Low serum cholesterol levels are an independent risk factor (Asano et al., 2008) and a high BMI at age 20 years is associated with an increased risk of death from stomach cancer (Tanaka et al., 2007). A high body weight may be especially important for middle third and nondifferentiated cancers (Inoue et al., 2002). Diabetes has been linked with stomach cancer among women (Inoue et al., 2006; Kuriki et al., 2007), but decreased risk in males has been reported (Khan et al., 2006). Serum glucose levels may (Jung et al., 2008) or may not (Jun et al., 2006) demonstrate an association, but it is a possible cofactor increasing the risk posed by *Helicobacter pylori* infection (Yamagata et al., 2005). Functional variants of insulin-like growth factor-binding protein-3 might be important markers for susceptibility (Chen et al., 2008b). General socioeconomic status is a complicating factor (Tran et al., 2005).

Protective influencess include intake of fruits and vegetables, as well as frequent physical exercise

(Kobayashi et al., 2002; Huang et al., 2004; Nan et al., 2005; Setiawan et al., 2005). Those who have very low plasma levels of alpha-carotene and beta-carotene are at a higher risk of gastric cancer (Persson et al., 2008b).Fish and soybean products appear benefical (Ito et al., 2003), and the erythrocyte composition of n-3 fatty acids was found to be negatively linked to risk (Kuriki et al., 2007). Ginseng intake might be a factor (Kamangar et al., 2007). With green tea, no clear evidence of a role in the prevention was noted in case control or meta-analyses of cohort studies (Koizumi et al., 2003; Zhou et al., 2008; Myung et al., 2009), but protective effects have been documented with modification by susceptibility genes (Mu et al., 2005) and it may be that only the distal portion is protected (Sasazuki et al., 2004). No association was found between serum 25(OH)-vitamin D and risk (Chen et al., 2008a).

Another possible explanation for the sex dependence is hormonal. Multiparity appears to confer a protective tendency on gastric cancer mortality, although this result is inconsistent with reports from elsewhere (Kaneko et al., 2003). Although early estrogen exposure may have some protective effect (Freedman et al., 2007;Persson et al., 2008a), female reproductive factors may have no substantial influence on gastric cancer development (Persson et al., 2008a).

Gastric cancer screening or factors associated with it are linked with lower mortality from gastric cancer (Lee et al., 2006; Miyamoto et al., 2007). Although stomach cancer screening is effective it is often underutilized, as for example in Korea (Hahm et al., 2008). Arguments have been made for use of *Helicobacter pylori* (Yokoyama et al., 2007; Yanaoka et al., 2008; Yeh et al., 2009) or low CagA IgG titer (Suzuki et al., 2007; Yokoyama et al., 2007) to identify high-risk groups. Alternatively, elevated serum pepsinogen levels can be applied (Yanaoka et al., 2008), subjects with severe atrophic gastritis needing regular examination regardless of infection (Sasazuki et al., 2006).

Colorectal Cancer

Cancers of the colon and rectum are particularly frequent in Japan but less common in China and Korea and rare in Mongolia, for the present (see Figure 8). Over the last 30 years there has been a continued increase in both sites in tandem in many registries, with a tendency for a plateau more recently (see Figures 9 and 10).

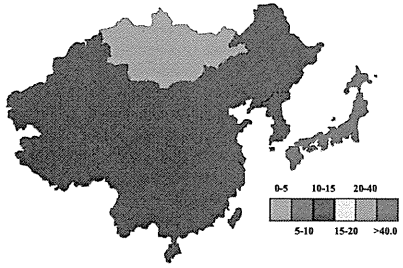

Figure 8. Male Colorectal Cancer Incidences/100,000 (Globocan, 2002: Ferlay et al., 2004)

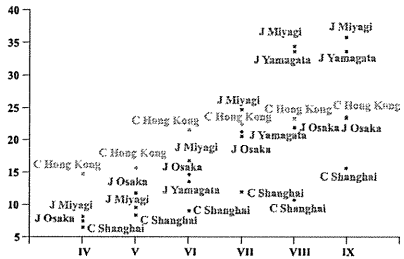

Figure 9. Male Colon Cancer Incidences/100,000 over Time (Waterhouse et al., 1982; Muir et al., 1987; Parkin et al., 1992; 1997; 2002; Curado et al., 2007)

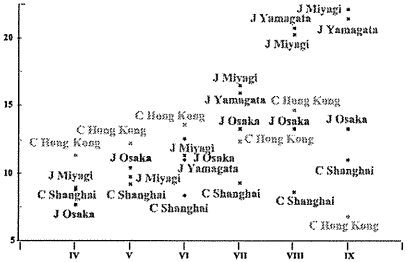

Figure 10. Male Rectal Cancer Incidences/100,000 over Time (Waterhouse et al., 1982; Muir et al., 1987; Parkin et al., 1992; 1997; 2002; Curado et al., 2007)

Improved diagnostic procedures with the spread of cancer screening might be responsible for some effects (Minami et al., 2006). With economic development there appears to be an increase in the colon to rectum ratios, these being particularly high in Hong Kong and consistently greater

Table 5. Colorectal Cancer*: Colon/Rectum Ratios

	Male			Female		
	Colon	Rectum	Ratio	Colon	Rectum	Ratio
Guangzhou	14.0	11.1	1.3:1	10.9	6.8	1.6:1
Hong Kong	23.8	7.0	3.4:1	18.9	4.2	4.5:1
Jiashan	9.8	10.7	0.9:1	8.7	9.0	1.0:1
Shanghai	15.8	11.2	1.4:1	14.6	8.3	1.8:1
Zhongshan	8.5	8.7	1.0:1	6.5	6.0	1.1:1
Busan	12.7	12.6	1.0:1	7.8	7.4	1.1:1
Daegu	13.5	15.2	0.9:1	9.1	8.9	1.0:1
Daejeon	16.7	17.7	0.9:1	8.8	9.8	0.9:1
Gwangju	14.6	12.6	1.2:1	8.9	8.5	1.0:1
Incheon	15.5	15.4	1.0:1	9.8	8.7	1.1:1
Jejudo	11.2	10.7	1.0:1	6.9	7.0	1.0:1
Seoul	18.7	17.4	1.1:1	11.5	9.7	1.2:1
Ulsan	14.8	12.1	1.2:1	9.9	8.6	1.2:1
Aichi	24.9	16.0	1.6:1	18.1	8.4	2.2:1
Fukui	27.2	16.9	1.6:1	19.6	8.2	2.4:1
Hiroshima	32.1	22.3	1.4:1	21.9	10.6	2.1:1
Miyagi	36.0	22.4	1.6:1	21.5	10.9	2.0:1
Nagasaki	27.2	19.5	1.4:1	17.1	10.0	1.7:1
Osaka	23.6	13.5	1.7:1	15.0	6.5	2.3:1
Yamagata	33.9	21.7	1.6:1	21.1	10.2	2.1:1

*Incidence data from Curado et al., 2007

in Japanese than otherwise in Chinese or Koreans, and more so in females than males (see Table 5). An increasing proportion of ascending and transverse colon cancer has been reported in China (Li and Gu, 2005) and a proximal shift has beem noted in China (Fengju et al., 2005) and Japan (Takada et al., 2002). In Korea changes in the colon-to-rectal ratio may mainly be due to an increase in left-sided colon cancer (Kim et al., 2002). Dietary risk factors appear to considerably differ between colon and rectal cancers (Wakai et al., 2006) and division may also be necessary for subsites within the colon (Moore et al, 2005). Colon cancer appears more closely associated than rectal cancer with environmental factors leading to obesity, and this association is more pronounced in men than in women (Nakaji et al., 2003). Rectal lesions in contrast appear more linked to alcohol consumption and tobacco smoking (World Cancer Research Fund, 1997; Shimizu et al., 2003; Toyomura et al., 2004; Mizoue et al., 2006).

Diet is clearly the major influence, although the inherent diversity makes drawing simple conclusions very difficult. For example both traditional Japanese and the Western dietary patterns have been found to be positively associated with colon cancer risk in females (Kim et al., 2005). However, the amount consumed overall may be a prime factor since there have been reports of association between BMI and adenomatous colonic polyps in Korean men (Lee et al., 2008; Lee et al., 2007) and colon cancer risk in men (Honjo et al., 1995; Shimizu et al., 2003), as well as obesity and excessive weight gain with risk of colon cancer death in Japanese women but not men (Tamakoshi et al., 2004b). Among women, the risk may be modified by menopause status, possibly through altered endogenous oestrogen levels (Hou et al., 2006). In Japan, Kono has argued that temporal change in fat and meat intake coincided with the incidence of colon cancer approximately 20 years later (Kono, 2004). Using a similar approach, Kuriki et al (2004) showed that colon cancer among Japanese might be closely associated with the increment in type II diabetes, reflecting westernization of food intake. Supportive evidence with regard to sigmoid colon adenomas was earlier provided by Kono et al (1998). The period of hyperinsulinemia which occurs prior to onset of diabetes could be an important risk factor (for reviews see Moore et al., 1998; Mori et al., 2000). In both Japan and Korea also the metabolic syndrome was found to be associated with colorectal adenoma, with abdominal obesity as an important risk factor (Morita et al., 2005; Kim et al., 2007). Higher plasma C-peptide may indicate a subsequent risk of colorectal cancer in Japanese men (Otani et al., 2006; 2007), although high serum CRP levels were not associated in the JACC Study (Ito et al., 2005). Sub-site distribution must be taken into account since serum insulin levels appear to best correlate with the presence of adenoma and hyperplastic polyps in the proximal colon (Yoshida et al., 2006). Findings of preventive potential for exercise (Hou et al., 2004; Isomura et al., 2006; Lee et al., 2007b) are in line with a role for the metabolic syndrome. However, it is not clear which sites are most affected, colon but not rectal being reported in one study (Takahashi et al., 2007) and all but the proximal colon in another (Isomura et al., 2006)

Fat intake was a risk factor in another study (Tokudome et al., 2000) and an ecological study showed positively associations with fat and oil intake in China (Yang et al., 2002). "Fat-bile acids" and "deficiency of dietary fibres" were reported to contribute to colon cancer etiology in Jiashan county (Wang et al., 2001) and increases in dietary fat and protein consumption may be behind the rising colon cancer rates in Shanghai (You et al., 2002). While no significant association between total meat consumption and the risk of any sub-site of colorectal cancer has been found (Sato et al., 2006; Kimura et al., 2007), meat effects may depend on metabolism of oxidized low-density lipoprotein and long-chain fatty acids (Kuriki et al., 2005). Increase in risk has been noted with processed meat (Oba et al., 2006) and dried/salted fish (Yang et al., 2003).

Association with plant protein consumption is generally inverse, as is also the case for carbohydrate and cereals/fibre (Hoshiyama et al., 2000; Yang et al., 2002; Mizoue et al., 2005; Wakai et al., 2007), although again with inconsistencies (Nakaji et al., 2001; Sato et al., 2005). This is also the case for dietary fibre. For example a prospective study in Japan reported an inverse association between fibre intake and colon cancer risk (Wakai et al., 2007), but another group did not find any dose dependent risk reduction (Otani et al., 2006). It has been argued that drastic reduction in cereals is one of the most important dietary factors determining the risk of colon cancer in Japan (Kono and Anh, 2000) and at the country level, we can also see a good inverse correlation with consumption of cereals (Tajima et al., 2002). Frequent raw/cooked fish intake may decrease the risk (Yang et al., 2003; Kimura et al., 2007) and has been related to PUFAs in erythrocyte membranes (Kuriki et al., 2006). Coffee consumption may lower the risk among Japanese women (Oba et al., 2006; Lee et al., 2007a), although not associated with the incidence in the general population in Japan (Naganuma et al., 2007). An inverse association with regular tea drinking was observed for both colon and rectal cancers in China (Yang et al., 2007) and green tea extract proved to be an effective supplement for the chemoprevention of metachronous colorectal adenomas (Shimizu et al., 2008), but other authors have noted no link between green tea and colorectal cancer (Nagano et al., 2001; Suzuki et al., 2005). Calcium and vitamin D may prevent colorectal carcinogenesis (Mizoue et al., 2008).

Data for smoking and alcohol are inconsistent. In China, they were not found to be risk factors for colorectal cancers in Shanghai, except with heavy heavy smokers for rectal and drinkers for colon (Ji et al., 2002). Similar findings were published for Jiashan County (Chen et al., 2006) and no smoking influence was concluded for Japan (Wakai et al., 2003). However, in Hong Kong associations between alcohol and colorectal and cigarette smoking and rectal cancer risk were reported (Ho et al., 2004) and the proportion of colorectal cancer attributable to alcohol consumption or smoking in Japan was estimated to be 46% (Otani et al., 2003). Alcohol associations have indeed been reaffirmed (Wakai et al., 2005; Otani et al., 2003; Mizoue et al., 2008). Significant increase in risk was noted for cancer of the distal colon and rectum, but not the proximal colon, in one case (Akhter et al., 2007). In another

investigation, male ex- or current drinkers demonstrated a two-fold risk for colon cancer compared with nondrinkers, whereas a link with the rectum was considered less likely (Mizoue et al., 2006). While a folate-rich status was not found to be preventive in Japan, this may have been due to an insufficient number of folate-deficient subjects (Otani et al., 2008). In China, adequate folate intake showed an inverse association with the risk of colon cancer, linked with MTHFR polymorphisms (Jiang et al., 2005; Cao et al., 2008). Protection by the MTHFR 677TT genotype was also noted in Japan (Yinet al., 2004). Polymorphisms of the ADH2 and ALDH2 genes are additionally significantly associated with risk in China (Gao et al., 2008). Gene-environmental interactions between the CYP2E1 polymorphism and smoking or alcohol drinking may further exist for colorectal neoplasia (Gao et al., 2007; Morita et al., 2008).

There are a number of other assorted factors. For example, constipation or laxative use increases the risk of colon cancer (Kojima et al., 2004; Watanabe et al., 2004) and drinking well water was identified as playing a role in China, especially for rectal cancer (Chen et al., 2005). Atrophic gastritis may increase the risk of rectal cancer (Machida-Montani et al., 2007). Reproductive history may (Tamakoshi et al., 2004a) or may not (Akhter et al., 2008) be of interest, and colon risk was found to be increased in Chinese women who used oral contraceptives for over 3 years (Rosenblattet al., 2004). A weak benefit of soy foods was found for women in Japan (Oba et al., 2007) but intake of isoflavones, miso soup, and soy food was without substantial influence in a more recent study of Japanese men and women (Akhter et al., 2008).

The fecal occult blood test for screening in Japan is associated with a major reduction in mortality from the disease (Lee et al., 2007c), although participation and compliance are low (Saito, 2006). In China, it has been concluded that standard FOBT plus colonoscopy is the best approach (Li et al., 2007), although immuno FOBT is more sensitive and cost effective (Li et al., 2006). Screening virtual colonoscopy is a satisfactory alternative for the detection of polyps greater than 10 mm (Wong et al., 2002) and is now attracting increasing interest (Iinuma, 2008).

Liver Cancer

Liver cancer is a major problem in Mongolia and China

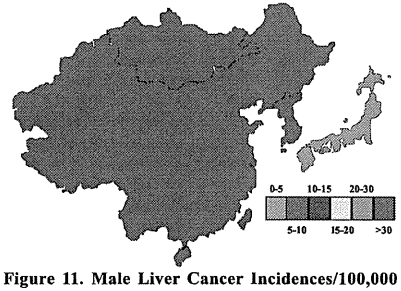

Figure 11. Male Liver Cancer Incidences/100,000 (Globocan, 2002: Ferlay et al., 2004)

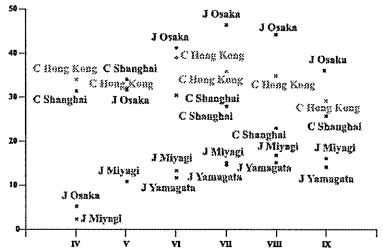

Figure 12. Male Liver Cancer Incidences/100,000 over Time (Waterhouse et al., 1982; Muir et al., 1987; Parkin et al., 1992; 1997; 2002; Curado et al., 2007)

and to lesser extents in Korea and Japan (see Figure 14). In both males and females by far the highest liver cancer incidence rates in Asia have been reported in Mongolia, presumably linked to a very high prevalence of both hepatitis B and C (Munkhtaivan et al., 2001). Rates are now generally decreasing in registries having long-term data (see Figure 15), with downward trends reported particularly in Tianjin (Hao et al., 2003) and Osaka, mainly because of decreased HCV-related tumours in the latter case (Tanaka et al., 2008). Hepatocellular carcinomas (HCCs) predominate in the majority of registries, but there may also be relatively high levels of cholangiocellular carcinomas (CCC), especially in Korean females (see Table 6).

In China, HBV appears to be the prime causal agent (Yu et al., 2002), being virtually ubiquitous in HCC patients, while HCV co-infection is present in about 10% of cases (Gao et al., 2005). High HBV DNA levels, particularly of subgenotype Ce, play important roles (Chan et al., 2008), but aflatoxin B (1) may also be involved (Li et al., 2001; Luo et al., 2005). Modest levels of exposure

Table 6. Liver Cancer Histopathology: HCC-CCC Percentages

	Male			Female		
	HCC	CCC	Ratio	HCC	CCC	Ratio
Guangzhou	92.1	2.1	43.9:1	86.3	3.4	25.4:1
Hong Kong	88.7	7.4	12.0:1	66.9	22.8	2.9:1
Jiashan	78.4	19.3	4.1:1	86.2	13.8	6.2:1
Shanghai	11.4	3.7	3.1:1	10.2	10.2	1.0:1
Zhongshan	47.9	3.1	15.5:1	37.3	13.4	2.8:1
Busan	67.7	21.9	3.1:1	46.2	39.7	1.2:1
Daegu	77.3	16.1	4.8:1	59.4	24.4	2.4:1
Daejeon	65.0	20.2	3.2:1	46.1	33.7	1.4:1
Gwangju	64.7	24.7	2.6:1	45.1	29.6	1.5:1
Incheon	64.7	22.9	2.8:1	47.0	39.5	1.2:1
Jejudo	74.4	18.3	4.1:1	45.2	32.3	1.4:1
Seoul	70.4	20.0	3.5:1	51.1	35.0	1.5:1
Ulsan	71.8	19.1	3.8:1	65.4	25.0	2.6:1
Aichi	90.8	7.9	11.5:1	83.6	14.2	5.9:1
Fukui	85.4	14.6	5.8:1	77.6	18.4	4.2:1
Hiroshima	90.2	7.5	12.0:1	85.7	11.5	7.5:1
Miyagi	80.6	12.3	6.6:1	64.2	21.9	2.9:1
Nagasaki	84.2	11.4	7.4:1	69.6	29.5	2.4:1
Osaka	94.4	4.8	19.7:1	90.5	8.4	10.8:1
Yamagata	76.7	14.5	5.3:1	61.7	23.4	2.6:1

*Incidence data from Curado et al., 2007

may triple the risk HBV-infected men (Ming et al., 2002). Although a HCV monoinfection pattern predominates in Mongolia (Kurbanov et al., 2007), co-infection with HBV and HDV has stronger associations with HCC development at younger age (Oyunsuren et al., 2006a). HBV and HCV are both independent risk factors for Korean HCCs (Shin et al., 1996). In Japanese, HCCs are also largely due to HCV, especially in birth cohorts around 1931-1935 (Tanaka et al. 2002; Mizokami and Tanaka, 2005; Tsukuma et al., 2005), but different HBV genotypes are also involved in many cases (Orito and Mizokami, 2003; Ohishi et al., 2008). Interactions of phenotype with the genotype have been suggested (Heneghan et al., 2003).

Additional factors are habitual alcohol drinking, betel quid chewing and cigarette smoking in Taiwan (Tsai et al., 2001; Wang et al., 2003) and tobacco Japan, the latter particularly for late stage HCC development (Hara et al., 2008), and heavy alcohol consumption and tobacco in Korea (Jee et al., 2004) and Japan (Luo et al., 2005;Ohishi et al., 2008; Tanaka et al., 2008). The MTHFR 677 C/T genotype is associated with an increased risk of primary liver cancer in a Chinese population (Mu et al., 2007). It has been estimated that tobacco is currently responsible for about 50,000 liver cancer deaths each year in China, chiefly among men with chronic HBV infection (Chen et al., 2003).

Obesity is also associated with HCC (Qian and Fan, 2005; Ohishi et al., 2008) and risk in patients with chronic hepatitis C increases in proportion to BMI (Ohki et al., 2008). Furthermore, diabetes mellitus is associated with increased hepatocellular carcinoma risk (Ohishi et al., 2008), mortality being greatly elevated with impaired glucose tolerance (Khan et al., 2006). A high level of serum glucose has been found to increase liver cancer risk independently of hepatitis infection and drinking history in Koreans (Gwack et al., 2007). A sex hormone involvement is suggested by influence of a genetic polymorphism in estrogen receptor 1 (Zhai et al., 2006). A recent metaanalysis also showed a positive association between *H. pylori* infection and the risk of HCC (Xuan et al., 2008).

At the same time, an inverse association between vegetable consumption and the risk of death from liver cancer has been reported (Pham et al., 2006) and coffee may be protective (Inoue et al., 2005; Kurozawa et al., 2005; Shimazu et al., 2005; Tanaka et al., 2007; Ohishi et al., 2008). Dietary items rich in protein, especially fresh fish, might similarly be beneficial (Yu et al., 2002) and consumption of miso soup and other soya foods may also reduce risk (Sharp et al., 2005). On the other hand, intake of eggs is significantly associated with increased HCC-associuated mortality in men (Kurozawa et al., 2004).

For prevention, vaccination of children is very effective (Chang et al., 2000), but even in adulthood it may reduce the likelihood of malignancy (Lee et al., 1998). In high risk cases, screening is also feasible. Testing for HCV and HBV began in 2002 in Japan, and consequent reduction of HCC is anticipated (Kiyosawa et al., 2004). High viral load is the major risk factor and effected individuals should be carefully monitored (Evans et al., 1998; Ohata et al., 2004). The anti-HCV titer may also be useful for mass screening (Hara et al., 2001) and α-fetoprotein serum levels are now employed for early detection and diagnosis in Mongolia (Oyunsuren et al., 2006b). However, in China, while screening with this marker resulted in earlier diagnosis of liver cancer, the gain in lead time did not result in any overall reduction in mortality, because therapy for the patients found by screening was ineffective (Chen et al., 2003).

Intrahepatic cholangiocellular carcinoma is associated with HBV infection and hepatolithiasis in China (Zhou et al., 2008). HCV-related cirrhosis is also a major risk factor for primary CCCs in Japanese patients (Kobayashi et al., 2000). In Shanghai, an HBV endemic area, chronic HBV infection was further linked with a 2.4-fold risk of extrahepatic bile duct cancer (Hsing et al., 2008). In additin, the parasite *Clonorchis sinensis* in stools and heavy drinking were earlier associated with the risk in Korea (Shin et al., 1996).

Gallbladder Cancer

Gallbladder cancer is relatively rare throughout the region from Cancer Incidence in Five Contintents data, the cancer not being separately covered in Globocan 2002. In Japan, rates now may be decreasing, with much higher incidences in traditional Yamagata than in Osaka (see Figure 13), this interestingly mirroring the situation with the proportion of CCs in the liver (see Table 6). Gallbladder cancer is also relatively frequent in Koreans, who feature cholangiocellular lesions as over one third of the total liver cancers.

Regarding risk factors, cholelithiasis is associated with both gallbladder and extrahepatic bile duct cancer, while obesity may increase the risk of the latter only (Ishiguro et al., 2008). In Taiwan, individuals with lower serum high-density lipoprotein level, diabetes and glucose intolerance are at high risk for developing gallstone disease (Chen et al., 1999) and also polyps (Chen et al., 1997). There are indications of roles for genetic variants involved in the regulation of obesity-related insulin sensitivity (Chang et al., 2008) and lipid metabolism (Andreotti et al., 2008). Aspirin use has been associated with a reduced risk (Liu et al., 2005), an inverse relationship also being reported for tea consumption (Zhang et al., 2006).

Most gallbladder cancer in Shanghai could be

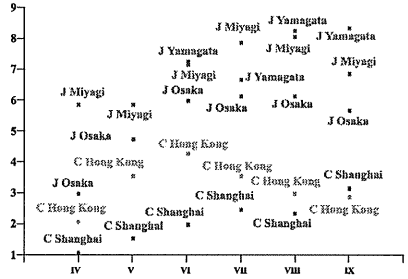

Figure 13. Male Gallbladder Cancer Incidences/ 100,000 over Time (Waterhouse et al., 1982; Muir et al., 1987; Parkin et al., 1992; 1997; 2002; Curado et al., 2007)

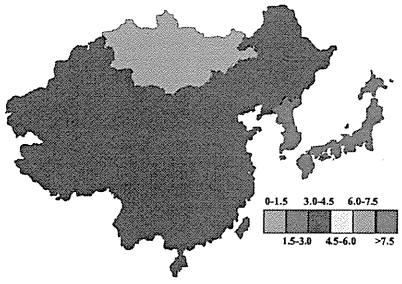

Figure 14. Male Pancreatic Cancer Incidences/100,000 (Globocan, 2002: Ferlay et al., 2004)

attributed to gallstones (Hsing et al., 2007) and variants in genes that influence inflammatory responses may predispose to both gallstones and biliary tract cancer (Hsing et al., 2008). In a prospective study in Japan, constipation and a history of hepatic disease were further found to elevate the risk of gallbladder cancer death (Yagyu et al., 2004). Alcohol and cigarette smoking may be etiological factors (Yagyu et al., 2008) and MGMT gene variants may alter susceptibility (Zhang et al., 2008). Base excision repair genes may further have an influence (Huang et al., 2008).

Pancreatic Cancer

Japan and Korea are both high incidence countries for pancreatic cancer, and equivalent rates are seen in some of the Chinese registries, although rates overall are intermediate (see Figure 14). Mongolia has a low level of the disease. Rates appear to be steady in Japan but may be increasing elsewhere, like Shanghai (see Figure 15). In Taiwan, a steeply increasing trend was found between 1975 and 1984 for both sexes, and then again in 1987-88 (Lin and Lee, 1992).

The main risk factors are cigarette smoking and/or elevated fasting serum glucose or a history of diabetes in Korea (Yun et al., 2006), Japan (Lin et al., 2002a) and China (Luo et al., 2007b). Men who report a history of diabetes mellitus and women with a history of gallstone/ cholecystitis are at significantly increased risk (Lin et al., 2002b). High serum levels of IGF-1 and IGFBP-3 may confer an increased risk of death from pancreatic cancer (Lin et al., 2004).

Folate-related enzyme polymorphisms appear to be genetic determinants (Wang et al., 2005), modifying the association with heavy alcohol consumption (Suzuki et al., 2008). No link has been found with total cholesterol, systolic blood pressure and body mass index in Korea (Oh et al., 2005; Berrington de Gonzalez et al., 2008), but BMI effects may differ according to sex and the period (Lin et al., 2007). Coffee may protect but not green tea (Luo et al., 2007a; Lin et al., 2008). There are no other clear links with diet reported except for high consumption of pickles perhaps increasing (Lin et al., 2006) and high vitamin C intake decreasing the risk of pancreatic cancer (Lin et al., 2005).

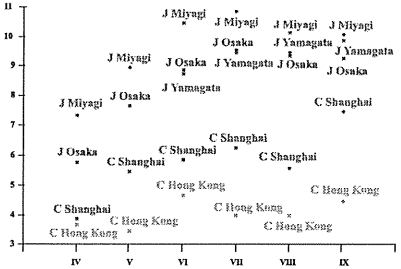

Figure 15. Male Pancreatic Cancer Incidences/100,000 over Time (Waterhouse et al., 1982; Muir et al., 1987; Parkin et al., 1992; 1997; 2002; Curado et al., 2007)

Pharyngeal and Laryngeal Cancer

Cancers of the pharynx and larynx are relatively infrequent in the region, with slightly higher rates in Korea (see Figure 16), except for the nasopharyngeal cancers (NPC) which are found in populations within southern China. While rates for laryngeal and NPC are decreasing in Hong Kong, generally there has been little change elsewhere. For example, the incidence of NPC does not appear to be decreasing in Sihui and Cangwu counties in southern China (Jia et al., 2006).

Cigarette smoking and alcohol drinking are well established as the major etiological influences on the oral cavity and pharynx (Ide et al., 2008). Alcohol may be a stronger risk factor for hypopharyngeal cancer than cigarette smoking (Takezaki et al., 2000), but tobacco ranks number one as risk factor in the larynx, with alcohol, insufficient intake of vegetable and fruits and air pollution as co-factors (Choi and Kahyo, 1991; Guo et al., 1995; Yun et al., 2005). Occupational exposure to asbestos and coal dust, and intake of salt-preserved meat and fish may also be important (Zheng et al., 1992).

DNA-repair gene expression may influence squamous cell carcinoma of the head and neck risk (Yang et al., 2005) and the GSTM1 null genotype is an important risk modifier for larynx cancer among Korean smokers (Hong et al., 2000). In line with roles for carcinogens, dietary antioxidant intake prevents head and neck squamous cell carcinoma in smokers and drinkers (Suzuki et al., 2006) and coffee consumption protects in the pharynx

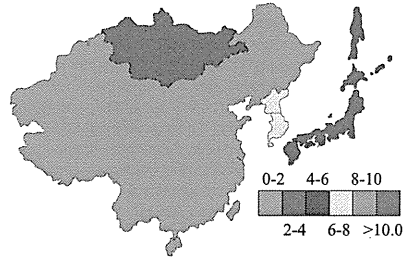

Figure 16. Male Laryngeal Cancer Incidences/100,000 (Globocan, 2002: Ferlay et al., 2004)

(Naganuma et al., 2008).

NPC tends to aggregate in Cantonese families in Guangdong Province (Jia et al., 2005) and a family history, higher education levels, salted fish and preserved vegetable intake, a history of chronic rhinitis are independent risk factors (Yuan et al., 2000a; Zou et al., 2000). Tobacco smoking and alcohol consumption, as well as exposure to high background radiation, were not significantly related to risk in one study (Zou et al., 2000), but other authors concluded that 12% of cases in Shanghai, China, were attributable to cigarettes (Yuan et al., 2000b). Occupational exposure to cotton dust, acids, and caustics, and work in dyeing and printing jobs in the textile industry may increase risk (Li et al., 2006) and the high prevalence in waiters/waitresses also points to an importance of indoor air quality (Yu et al., 2004) In contrast, high intake of oranges/tangerines was associated with a statistically significant reduction in risk (Yuan et al., 2000a) . Roles for carcinogens are suggested by an influence of DNA repair (Cao et al., 2006; Yang et al., 2007) and for inflammation by a link with cytokines (Zhu et al., 2008).

Lung Cancer

Lung cancer continues to be a major problem (see Figure 17), although rates are not generally increasing and are falling in sites like Hong Kong (see Figure 18). This appears attributable to a decrease in squamous cell, small cell and large cell carcinoma, while the incidence of adenocarcinoma increased until 1988-1990 and then

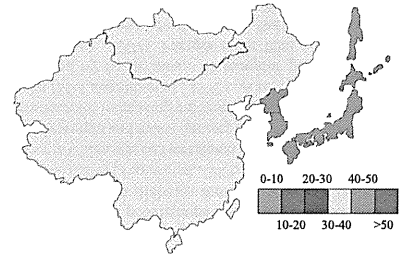

Figure 17. Male Lung Cancer Incidences/100,000 (Globocan, 2002: Ferlay et al., 2004)

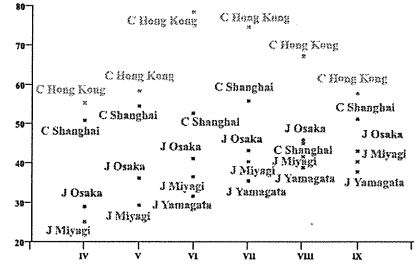

Figure 18. Male Lung Cancer Incidences/100,000 over Time(Waterhouse et al., 1982; Muir et al., 1987; Parkin et al., 1992; 1997; 2002; Curado et al., 2007)

Table 7. Lung Cancer Histopathology: SCC-AC Percentages

	Male			Female		
	SCC	AC	Ratio	SCC	AC	Ratio
Guangzhou	35.6	42.2	0.8:1	15.3	65.9	0.2:1
Hong Kong	25.6	36.1	0.7:1	9.7	60.7	0.2:1
Jiashan	51.3	40.5	1.3:1	20.3	72.9	0.3:1
Shanghai	7.6	8.0	1.0:1	2.9	14.2	0.2:1
Zhongshan	25.4	23.7	1.1:1	12.3	46.7	0.3:1
Busan	54.8	28.0	2.0:1	17.9	57.9	0.3:1
Daegu	47.7	25.9	1.8:1	20.0	58.1	0.3:1
Daejeon	44.3	26.7	1.7:1	19.1	57.9	0.3:1
Gwangju	49.3	24.9	2.0:1	16.3	56.8	0.3:1
Incheon	44.5	28.3	1.6:1	15.4	62.6	0.2:1
Jejudo	42.5	26.2	1.6:1	18.1	57.8	0.3:1
Seoul	41.8	30.2	1.4:1	15.0	62.0	0.2:1
Ulsan	40.7	24.4	1.7:1	21.9	52.1	0.4:1
Aichi	27.2	49.1	0.6:1	8.2	80.6	0.1:1
Fukui	34.8	42.8	0.8:1	8.9	76.8	0.1:1
Hiroshima	32.2	47.0	0.7:1	9.9	76.9	0.1:1
Miyagi	32.8	37.6	0.9:1	8.3	72.0	0.1:1
Nagasaki	30.7	42.9	0.7:1	8.0	75.4	0.1:1
Osaka	32.0	40.0	0.8:1	13.8	62.9	0.2:1
Yamagata	38.6	38.0	1.0:1	9.8	73.8	0.1:1

Data from Curado et al., 2007

stabilized (Au et al., 2004). In Hong Kong females, incidences increased steadily up to 1990, but thereafter, a downward trend was observed, an age-cohort model providing the best description of the data with domestic air pollution, poor nutrition and tobacco smoking as important risk factors (Chiu et al., 2004). A birth cohort effect has also been noted in Japan (Takahashi et al., 2001). In Tianjin asignificant increasing trend of incidence rates of lung cancer was noted from 1981 to 1990, with little change thereafter (Chen et al., 2006). A tendency for decrease has been noted in Shanghai (Liao et al., 2007). However, the future is not clear and application of a Bayesian age-period-cohort model to the National Vital Statistics data from 1952 to 2001 suggested that the number of deaths due to lung cancer in Japan will double for men and women during the next 3 decades due to the aging of the baby-boomer generation, so that currently declining trends in some age groups will reverse (Kaneko et al., 2003). The situation is complicated by the shift to adenocarcinomas (Sobue et al., 1999), which are on the increase (Yoshimi et al., 2003), and possibly linked to air pollution in Korea (Hwang et al., 2007) and Taiwan (Liaw et al., 2008). Comparison of the ratios of SCCs to ACs is very revealing (see Table 7), Japanese being exceptional in having more of the latter, especially in females.

The major risk factor is male tobacco smoking (Tajima et al., 2000; Wakai et al., 2006; Bae et al., 2007), quitting bringing about reduction in risk (Lam et al., 2007) even in those over 65 (Wakai et al., 2007), although size of risk reduction may be disproportionately smaller than that expected from the reduced amount of cigarette consumption (Song et al., 2008). In one study risk elevation due to smoking was 12.7 and 17.5 fold for squamous cell carcinoma and small cell carcinoma, while for adenocarcinoma it was only 2.8 times (Sobue et al., 2002).

Furthermore, after cessation, change in odds ratios is much higher for SCC than AC (Sobue et al., 2002). Squamous cell carcinoma and small cell carcinoma were earlier 2.5-3.3 times higher in Osaka and Okinawa compared to Nagano, while adenocarcinomas were almost equal in the 3 areas (Sobue et al., 2000). However, in Korean men, cigarette smoking appears as important for adenocarcinoma as for squamous cell carcinoma (Yun et al., 2005). Furthermore, passive smoking is a risk factor for adenocarcinoma among Japanese women (Kiyohara et al., 2003; Kurahashi et al., 2008).

Data for poly-morphisms in carcinogen metabolising and DNA repair enzymes point to roles for tobacco carcinogens in both smokers (Park et al., 2002; Osawa et al., 2007; Yang et al., 2007; Shi et al., 2008; Ma et al., 2009) and non-smokers (Kiyohara et al., 2003; Chan-Yeung et al., 2004; Jung et al., 2006; Chen et al., 2009; Yin et al., 2009). The marked difference between Japan and USA lung cancer rates may be linked to higher efficiency of filters on Japanese cigarettes, lower levels of carcinogenic ingredients and lung-cancer-resistant hereditary factors among Japanese males (Marugame et al., 2004; Takahashi et al., 2008). In addition, smokers in Japan may initiate smoking at an older age and smoke fewer cigarettes per day for shorter durations (Marugame et al., 2005). One proposed reason for the shift towards ACs is a change in the type of cigarette smoked, but among subjects aged 65 years or more, there were no related differences in histological type, implying roles for other influences (Marugame et al., 2004).

Other risk factors may be chronic inflammation due to tuberculosis (Galeone et al., 2008; Engels et al., 2009) or damage due to coal (Tian et al., 2008) or cooking oil pollution (Yu et al., 2006; Li et al., 2008). Female restaurant workers have a greater oxidative stress response to cooking oil fumes than male restaurant workers, providing additional evidence of the link between lung cancer in Chinese women (Pan et al., 2008). It is further noteworthy that change to portable stove use has been linked with lower lung cancer mortality in rural Chinese (Hosgood et al., 2008). A meta-analysis confirmed an association between lung cancer and indoor air pollution in Chinese (Zhao et al., 2006) and long-term exposure was significantly associated with female lung cancer in 7 Korean metropolitan cities (Hwang et al., 2007). Findings for growth factor receptor and transcription factor polymorphisms are also in line with inflammation as a major etiological factor (Jang et al., 2005; Choi et al., 2007). However, carcinogens are also important, like inorganic arsenic and polycyclic hydrocarbons in Chinese miners and pottery workers (Chen et al., 2007). In high incidence Xuanwei, food contamination by environmental polycyclic aromatic hydrocarbons may contribute (Shen et al., 2008). A high prevalence of HPV in lung carcinomas has been reported in the central part of China (Wang et al., 2008).

As expected, fruit and raw vegetables may play an important role (Ho et al., 2006; Matsuo et al., 2008) especially in protecting smokers from lung cancer (Gao et al., 2002), although not all findings are consistent (Liu et al., 2004). Furthermore there is no evidence that green tea consumption is preventive (Li et al., 2008). Cooked/raw fish consumption lowers the risk of adenocarcinoma (Takezaki et al., 2001; 2003).

Epidemiologic evidence on any association between alcohol drinking and lung cancer risk remains insufficient in terms of both the number and methodological quality of studies among the Japanese population (Wakai et al., 2007). Consumption was not found to be an independent risk factor in Japan (Nishino et al., 2006; Shimazu et al., 2008) or Korea (Bae et al., 2007). However, MTHFR genotypes might have a role especially among heavy smokers and drinkers (Suzuki et al., 2007). Regarding sex hormone influence, early age at menarche or late age at menopause significantly increased risk of lung cancer in one study (Liu et al., 2005) and later age at menopause, longer reproductive period, higher parity, and intrauterine device use were found associated with decreased risks in Shanghai women non-smokers (Weiss et al., 2008). Diabetes is a risk factor for lung cancer among women (Kuriki et al., 2007) and high fat consumption may increase the risk of lung cancer, especially that of adenocarcinoma in females (Ozasa et al., 2001). Paradoxically, adulthood BMI loss was found to significantly elevated the risk for lung cancer mortality among current smokers (Kondo et al., 2007).

Regarding control strategies, knowledge of smoking is largely associated with education, but opinions on tobacco control are dependent on both smoking status and education (Nishi et al., 2005). Assigning a high priority to tobacco control in municipal health promotion activities was found to be significantly associated with implementation of school tobacco-control policies (Kayaba et al., 2005). In Japan, lung cancer screening has been estimated to reduce mortality from lung cancer by approximately 60% (Tsukada et al., 2001), 41% (Nishii et al., 2001) and 46% (Sagawa et al., 2001). Targeting those with a family history might be recommended (Nitadori et al., 2006).

Kidney Cancer

Kidney carcinoma rates in the area are moderate (see Figure 19), although in Japan they are equivalent to those in Japanese in the US, and in the Hokkaido region particularly high (Marumo et al., 2001). Generally now a plateau in Miyagi and decrease in Osaka and Yamagata

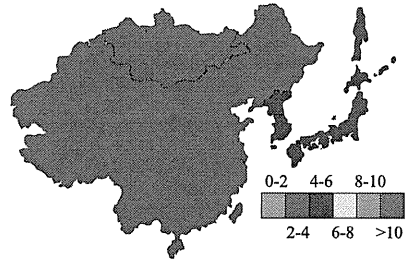

Figure 19. Male Kidney Cancer Incidences/100,000 (Globocan, 2002: Ferlay et al., 2004)

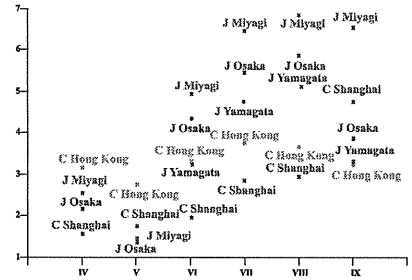

Figure 20. Male Kidney Cancer Incidences/100,000 over Time (Waterhouse et al., 1982; Muir et al., 1987; Parkin et al., 1992; 1997; 2002; Curado et al., 2007)

(see Figure 20) but increase in Shanghai and in the past in Korea (Song et al., 2008).

Obesity has been associated with an increased risk of kidney cancer in postmenopausal Korean women (Song et al., 2008) and diabetes mellitus is a risk factor in Japanese males (Inoue et al., 2006). Furthermore, kidney cancer in China was earlier related to increasing categories of body weight and meat consumption, while reduced risks were seen for increasing categories of fruit and vegetable intake (McLaughlin et al., 1992). A role for vitamin D is suggested by an influence of receptor polymorphisms (Obara et al., 2007). Factors other than arsenic water contamination may contribute to the unusually high

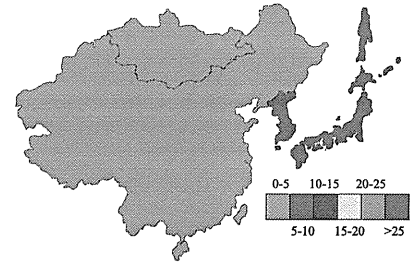

Figure 21. Male Urinary Bladder Cancer Incidences/ 100,000 (Globocan, 2002: Ferlay et al., 2004)

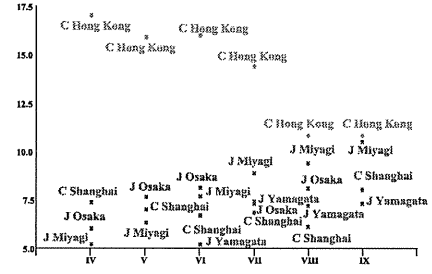

Figure 22. Male Urinary Bladder Cancer Incidences/ 100,000 over Time (Waterhouse et al., 1982; Muir et al., 1987; Parkin et al., 1992; 1997; 2002; Curado et al., 2007)

incidence of ureter cancer in the "non-blackfoot disease" area in Taiwan (Yang et al., 2002). About 20% of lesions are non-adenocarcinomas in all of the registries.

Time dependent development of malignancy occurs in recipients of renal transplants (Imao et al., 2007) and long-term dialysis is a risk factor for renal cell carcinoma (Satoh et al., 2005). Such dialysis cases have a better survival when regularly screened (Ishikawa et al., 2004).

Urinary Bladder Cancer

Urinary bladder incidences at the country levels are relatively low (see Figure 21), although high rates have been recorded in Hong Kong. Incidences are now slightly increasing, again with the exception of Hongkong (see Figure 22). Since up to 60% of papillary bladder lesions in Hong Kong have been found to be positive for human papilloma virus, there is an intriguing possibility that changes in levels of infection may be involved (Chan et al., 1997).The incidence rate of all urological cancers (except urethral and penile cancer) has increased remarkably, especially in the last several years in Korea (Cheon et al., 2002). In all of the countries, transitional cell carcinomas account for the vast majority of cases.

Tobacco is the accepted risk factor for transitional bladder (Wada et al., 2001; Yun et al., 2005), with roles for CYP4B1 genotypes (Sasaki et al., 2008) and DNA repair enzyme polymorphisms (Shao et al., 2007; Arizono et al., 2008). Fruit and green-yellow vegetable intake may be protective (Nagano et al., 2000; Wakai et al., 2000; 2004) as well as soy (Sun et al., 2004), while eggs and meat could have etiological roles, along with excessive green tea consumption (Wakai et al., 2000; 2004).

Other reported risk factors are bronchial asthma and tuberculosis in Korea (Kim et al., 2000), high arsenic levels in drinking water (Guo et al., 1997; Khan et al., 2003; Huang et al., 2008), petrochemical air pollution (Tsai et al., 2009), and trihalomethane and nitrate in drinking water (Chang et al., 2007; Chiu et al., 2007). The urinary bladder incidence in parts of Taiwan declined after improvement of the drinking water supply system (Yang et al., 2005). A significant protective effect of magnesium intake has also been documented (Yang et al., 2000).

Prostate Cancer

Prostate cancer incidences are very low in all of North-

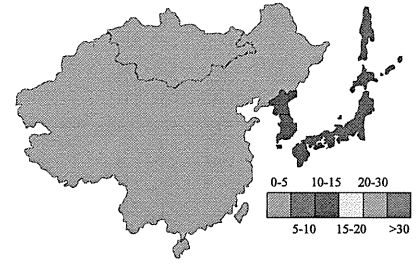

Figure 23. Prostate Cancer Incidences/100,000 over Time(Globocan, 2002: Ferlay et al., 2004)

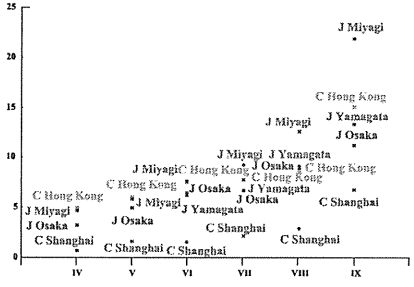

Figure 24. Prostate Cancer Incidences/100,000 over Time (Waterhouse et al., 1982; Muir et al., 1987; Parkin et al., 1992; 1997; 2002; Curado et al., 2007)

west Asia other than Japan and Korea (see Figure 23), but again there is considerable variation across registries, with considerable numbers of lesions seen in Hong Kong and Miyagi. Rates are increasing (see Figure 24) and this is apparently not due to screening, at least in Japan (Wakai, 2005). Rather the continued increase might be due to change in diet, increasing consumption of dairy products and decrease in soy and other traditional playing a role (Lee et al., 2003; Sonoda et al., 2004; Kurahashi et al., 2007; 2008a; 2008b; Li et al., 2008). Serum genistein, daidzein and equol seem to dose-dependently reduce prostate cancer risk (Ozasa et al., 2004), perhaps because of effects on serum estrone levels (Nagata et al., 2001). Androgen receptor polymorphisms exert an influence (Liu et al., 2004). The ability to produce equol or equol itself may be closely related to the low incidence of prostate cancer in the region (Akazu et al., 2002; 2004). Since higher consumption of soybeans and green tea is strongly related to the establishment of a capacity for equol production (Miyanaga et al., 2003), recent change in dietary habits resulting in low incidence of equol production in the young generation is a major potential risk factor for prostate cancer, not only in Japan but also in Korea (Fujimoto et al., 2008). The need for collaboration across the region has therefore be stressed (Akazu et al., 2007). Furthermore,since comparative geographic pathologic autopsy studies have suggested that rates for asymptomatic precancerous lesions may not differ markedly between Japan and the US, promoting factors for progression of prostate cancer may be of prime importance (Watanabe et al., 2000). Therefore rapid change in incidence rates is conceivable.

Elevated serum insulin levels may influence the risk of prostate lesions in Chinese men (Hsing et al., 2001) and abdominal adiposity may be associated with an increased likelihood of clinical cancer (Hsing et al., 2000). Gene polymorphisms of lipoprotein lipase (LPL) could play a a role (Narita et al., 2004). Physical activity may (Jian et al., 2005) or may not (Lacey et al., 2001) be preventive. While body mass index and height were not found to be significantly associated with risk of prostate cancer (Kurahashi et al., 2006), pointers to an importance of early-life factors have been obtained (Minami et al., 2008).

Protective influence in Asian countries has been reported for garlic and other allium vegetables (Hsing et al., 2002) and an inverse relation was observed between fish intake and the risk of prostate cancer, limited to those over 70 (Sato et al., 2008). While low fat local vegetarian food may have a protective effect against prostate carcinoma in thin Taiwanese (Chen et al., 2005), consumption of milk, fruits, all vegetables, green-yellow vegetables, and tomatoes showed no association in Japan (Allen et al., 2004; Sonoda et al., 2004). Vitamin D is not of importance, as judged by the lack of any significant relationship with receptor polymorphisms (Liu et al., 2003). In addition, no link between green tea and prostate cancer risk was found in one study of Japanese men (Kikuchi et al., 2006), although dose-dependent protection was evident in another (Jian et al., 2004), and there may be some specificity for advanced lesions (Kurahashi et al., 2008d). Regarding other factors, hemodialysis patients may be at increased risk (Kurahashi et al., 2008c) and longer sleep duration could be protective (Kakizaki et al., 2008). In this context, the fact that rotating-shift workers are significantly at risk is of interest (Kubo et al., 2006). In Taiwan, prostate cancer incidence declined gradually after improvement in the drinking water supply system (Yang et al., 2008). Carcinogen involvement is suggested by findings for CYP1A1 and CYP2E1 genotypes with a smoking or drinking habit (Yang et al., 2006).

Prostate cancer screening using PSA as a primary screening parameter during general health checkups has been proposed as very useful for efficiently detecting early-stage prostate cancer (Uchida et al., 2000). However, the estimated cancer detection rate in Korean men 55 years or older was 3.36% (Song et al., 2008), suggesting considerable overdiagnosis. In addition, International Prostate Symptom Score Symptomatic Japanese men are not at higher risk of prostate cancer despite their higher PSA values compared with asymptomatic men of the same age group (Matsubara et al., 2006). There has been no familial tendency for prostate cancer found in China (Bai et al., 2005) and criteria for high risk groups have yet to be determined.

Testis Cancer

Uniformly low incidences of testis cancer are apparent across the region, without any appreciable change over time in CIV data.

Breast Cancer

While breast cancer incidences in the region are generally relatively low, especially in Mongolia (see Figure 25), high rates are already evident in some registries, like Hong Kong and Miyagi. They are rising independent of geography (see Figure 26). For example, in China the incidence is expected to increase from 10-60 cases to more than 100 new cases per 100,000 women aged 55-69 years by 2021 (Linos et al., 2008). In Hong Kong, it is estimated that rates will continue to rise by approximately 1.1% per annum over the next 15 years (Wong et al., 2007). In Korea, the evidence points to a 2- to 3-fold increase in incidence and mortality by 2020 (Choi et al., 2005; Yoo et al., 2006). Age-period-chort modelling in Hong Kong has also

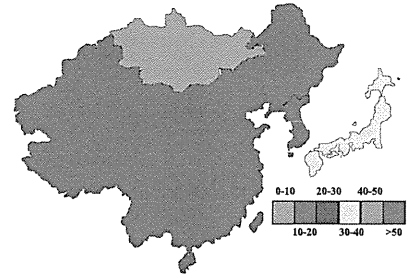

Figure 25. Female Breast Cancer Incidences/100,000 (Globocan, 2002)

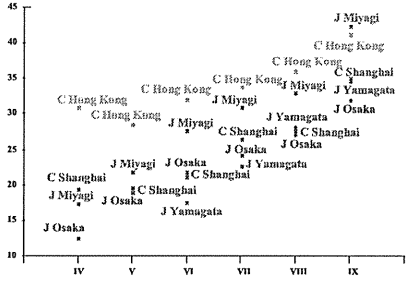

Figure 26. Female Breast Cancer Incidences/100,000 over Time (Waterhouse et al., 1982; Muir et al., 1987; Parkin et al., 1992; 1997; 2002; Curado et al., 2007)

revealed the incidence rate increase to be predominantly a cohort effect (Leung et al., 2002) and the same conclusion has been drawn in Japan (Minami et al., 2004).

In North-east Asia, epidemiologic studies have shown that early menarche, late menopause, late full-term pregnancy, and never having had a breast-fed child are primary risk factors in the development of both breast cancer (Suh et al., 1996; Yoo et al., 2002; Hirose et al., 2003b; Tamakoshi et al., 2005; Kim et al., 2007). In China, earlier menarcheal age, nulliparity, and later age at first live birth appear associated with increased risk of breast cancer among both pre- and post-menopausal women, while never having breast-fed and later age at menopause were associated with elevated risk only among post-menopausal women. (Gao et al., 2000). Lifestyle variables that reduce age at menarche may particularly contribute to the rising risk of breast cancer diagnosed after age 40 in Hong Kong (Leung et al., 2008). The evidence all points to an overwhelming role for estrogen exposure, as also supported by findings for estrogen-metabolizing genes and estrogen receptors (Shen et al., 2006), as well as genetic polymorphisms in CYP17 and CYP 19 (Hirose et al., 2004; Shin et al., 2005; Chen et al., 2008) and SULT (Choi et al., 2005). There may also be interaction between exposure to estrogens and MTHFR variants (Lin et al., 2004).

The importance of estrogen is further underlined by the effects of isofavones. While one recent prospective study suggested that consumption of soy food had no protective influence (Nishio et al., 2007), a meta-analysis provided support for the hypothesis that soyfood intake may be associated with a decreased risk (Qin et al., 2006). An earlier prospective study in Japan pointed to the same conclusion (Yamamoto et al., 2003), with inverse associations between isoflavone exposure and plasma genistein and breast cancer (Lampe et al., 2007; Iwasaki et al., 2008). Protective effects of soy may be greatest for ER+/PR+/HER2- tumors (Suzuki et al., 2008). A negative correlation between HRT use and breast cancer has been reported in Japan (Saeki et al., 2008).

The differentiation status of the breast is clearly important, as evidenced by protective effects of prolonged lactation (Yoo et al., 1992; Zheng et al., 2000; Lee et al., 2003). High mammographic density is a risk factor in Japan (Nagao et al., 2003; Nagata et al., 2005) especially in postmenopausal cases (Kotsuma et al., 2008).

Weight gain and central obesity are strong predictors for the risk of breast cancer among postmenopausal women (Chow et al., 2005; Wu et al., 2005; Li et al., 2006; Jee et al., 2008; Song et al., 2008), perhaps particularly for ER+ lesions (Iwasaki et al., 2007). Obesity can impact on the influence of reproductive factors (Hsieh et al., 1990) and there are clear associations with levels of steroid hormones and steroid hormone binding protein (Yoo et al., 1998). However the link might also be partly explained by influence on adiponectin levels (Miyoshi et al., 2003), but apparently not leptin (Woo et al., 2006), as well as plasma insulin (Hirose et al., 2003). The IGF axis may be important (Deming et al.,2008) and physical activity may reduce breast cancer risk through both hormonal and nonhormonal pathways (Adams et al., 2006;Suzuki et al., 2008).

High carbohydrate intake and a diet with a high glycemic load could be a risk factor (Wen et al., 2009), while a 'prudent' dietary pattern is negatively associated with breast cancer risk (Do et al., 2007; Hirose et al., 2007), with protective roles for antioxidant vitamins such as beta-carotene, lycopene and vitamin C intake (Do et al., 2003; Huang et al., 2007), green tea (Inoue et al., 2001; Shrubsole et al., 2009), mushrooms (Hong et al., 2008) and n-3 fatty acids and fish (Hirose et al., 1995; 2003; Shannon et al., 2007; Zhang et al., 2007). High erythrocyte compositions of specific fatty acids derived from fish intake have in fact been found to be associated with a lower risk of breast cancer (Kuriki et al., 2007).

There is evidence that environmental contaminants may be playing a role, and geographic clustering of residence in early life has pointed to early exposures related to breast cancer risk (Han et al., 2004). The association with older paternal age might point to an influence of genetic damage (Choi et al., 2005). Serum organochlorines could interact with genetic polymorphisms of glutathione S-transferase T1 (Chang et al., 2008) and a contribution of DNA repair enzymes has been documented (Lee et al., 2007; Li et al., 2008). However, smoking may not be important, at least in Japan (Lin et al., 2008) ,and evidence of alcohol risk, while present (Park et al., 2000; Choi et al., 2003b; Kim et al., 2004), is not conclusive (Nagata et al., 2007). Interactions between the MTRR A66G polymorphism and folate intake may exert an influence