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 degrees 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.

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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 CI5

<table>
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<th>Volume</th>
<th>I</th>
<th>II</th>
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¹UICC-ARO, ²apocpcontrol@yahoo.com ³National Cancer Center, Tokyo, ⁴National Office for Cancer Prevention and Control, Beijing, ⁵Jiangsu province Institute of Cancer Research, Nanjing, ⁶Taiwan Cancer Registry, College of Public Health, National Taiwan University, Taipei, ⁷International Medical Center of Japan, Tokyo, ⁸Cancer Registry, National Cancer Center, Ulanbataar, ⁹Korea Central Cancer Registry, National Cancer Center, Goyang/Seoul, ¹⁰Aichi Cancer Center, Nagoya, ¹¹Seoul National University, Seoul
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
### Table 3. Population-based Cancer Incidence/100,000 Data for North-East Asians - Females*

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<td>0.1</td>
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<tr>
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<td>1.9</td>
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<td>1.3</td>
<td>0.6</td>
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<tr>
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<td>16.5</td>
<td>20.2</td>
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<tr>
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<td>9.4</td>
<td>32.1</td>
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<tr>
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<tr>
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<td>8.7</td>
<td>10.7</td>
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<tr>
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<td>3.5</td>
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<tr>
<td>Leukemia</td>
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</tr>
<tr>
<td>Total</td>
<td>265</td>
<td>181</td>
<td>205</td>
</tr>
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</table>

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

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*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 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 Hawaiian 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 arsenicism 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). Oesophageal adenocarcinoma also declined among both males and females, even more than for oesophageal squamous cell carcinoma, so that the relative ratio decreased (Yee et al., 2007).

While the vast majority of oesophageal 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 infection by Helicobacter pylori were all found to be significant risk factors in Huaiwa (Wang et al., 2006).

Increased consumption of vegetables, fruits, seafood, tea and milk were found to be protective against the development of oesophageal 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 oesophageal and stomach cancers in a low-epidemic area, counteracting similar exposure levels of risk factors like pickled vegetables salty fish, leftover gruel and 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 oesophageal adenocarcinoma (Wu et al. 2003). A number of studies have focused on possible links with HPV, infection being high in oesophageal carcinomas of Henan emigrants, local residents and patients in Hubei Cancer Hospital (Yao et al., 2006). Viruses were also found in 30% of Kazakh oesophageal 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., 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 all increase the risk of esophageal cancer (Takezaki et al., 2001; Gao et al., 2002; Fan et al., 2008).

Table 4. Oesophageal Cancer Histopathology: SCC-AC Percentages

<table>
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<th>AC</th>
<th>SCC Female</th>
<th>AC</th>
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<td>90.7</td>
<td>4.9</td>
<td>18.5:1</td>
<td>86.0</td>
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</tbody>
</table>

*Incidence data from Curado et al., 2007
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 appear 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., 2008; Gwack et al., 2006). Korean and Japanese gastritis is reported to be characterized by more male- and antrum-predominant acute foveolitis (Lee et al., 2005). Major contributions for inflammation are further 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 influences include intake of fruits and vegetables, as well as frequent physical exercise.
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)

Table 5. Colorectal Cancer*: Colon/Rectum Ratios

<table>
<thead>
<tr>
<th></th>
<th>Male Colon</th>
<th>Male Rectum</th>
<th>Male Colon/Rectum Ratio</th>
<th>Female Colon</th>
<th>Female Rectum</th>
<th>Female Colon/Rectum Ratio</th>
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<td>11.1</td>
<td>1.3:1</td>
<td>10.9</td>
<td>6.8</td>
<td>1.6:1</td>
</tr>
<tr>
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<td>23.8</td>
<td>7.0</td>
<td>3.4:1</td>
<td>18.9</td>
<td>4.2</td>
<td>4.5:1</td>
</tr>
<tr>
<td>Jiashan</td>
<td>9.8</td>
<td>10.7</td>
<td>0.9:1</td>
<td>8.7</td>
<td>9.0</td>
<td>1.0:1</td>
</tr>
<tr>
<td>Shanghai</td>
<td>15.8</td>
<td>11.2</td>
<td>1.4:1</td>
<td>14.6</td>
<td>8.3</td>
<td>1.8:1</td>
</tr>
<tr>
<td>Zhongshan</td>
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<td>8.7</td>
<td>1.0:1</td>
<td>6.5</td>
<td>6.0</td>
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<tr>
<td>Busan</td>
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<td>7.8</td>
<td>7.4</td>
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<td>8.9</td>
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</tr>
<tr>
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<td>8.8</td>
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<td>1.2:1</td>
<td>8.9</td>
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<td>1.2:1</td>
</tr>
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<tr>
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<td>2.2:1</td>
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<tr>
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<td>1.6:1</td>
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</tr>
<tr>
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<td>1.6:1</td>
<td>21.1</td>
<td>10.2</td>
<td>2.1:1</td>
</tr>
</tbody>
</table>

*Incidence data from Curado et al., 2007

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
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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 been 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 menopausal 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 hyperinsulinaemia 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 (Oka 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 preventative 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 (Machu-DaMontani 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 (Rosenblatt et 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., 2006). and is more sensitive and cost effective (Li et al., 2007). Although immuno FOBT may exist for colorectal neoplasia (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).

Liver Cancer
Liver cancer is a major problem in Mongolia and China.
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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.,
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 (Ohi Ki 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-
associated 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
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
addition, 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 Continents 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)
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-I 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).

**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.
Lung Ne et al (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 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 (Liau 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 (Ba e 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)
(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 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 Hong Kong (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-
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 (Li 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 geographic variation (see Figure 26). For example, in China the incidence is estimated to increase from 10-60 cases to more than 100 new cases per 100,000 women aged 55-69 years by 2021 (Lin 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-cohort modelling in Hong Kong has also

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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)
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 (Miyoishi 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 betacarotene, lycopene and vitamin C intake (Do et al., 2007; Hirose et al., 2007; Sankaranarayanan 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

The importance of estrogen is further underlined by the effects of isoflavones. 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 soy food 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).
Benign breast disease is a likely risk factor (Dorjgochoo et al., 2008) and inflammation clearly could play an important role, with suggestions of COX-2 and TGF-beta/TNF-beta contributions to the etiology of mammary neoplasia (Lee et al., 2005; Gao et al., 2007). Stress also might impact on risk, having “ikigai” (life power) decreasing (Wakai et al., 2007) and short sleep duration elevating the likelihood of breast cancer (Kakizaki et al., 2008). Whether melatonin could act as an intervening factor between light exposure at night and serum concentrations of estrogen remains unclear (Nagata et al., 2008).

With regard to screening, there have not been any randomised control trials of mammography in the region, although biennial mammographic screening starting at age 50 years is being recommended, for example in Korea (Woo et al., 2007), but not Hong Kong and other Asian populations with low breast cancer prevalence (Leung et al., 2007). Earlier studies in Japan did point to screening reduction of mortality (Kuroishi et al., 2000). One problem is compliance and women in the contemplation stage need specific and correct knowledge delivered by diverse materials, reminders, and the inclusion of husbands as facilitators (Park et al., 2007). Breast surgery is relatively straightforward and surgical volume of hospitals does not appear to generally affect the 10-year survival rate from breast cancer significantly (Nomura et al., 2006).

Ovarian Cancer

Ovarian cancer is relatively infrequent in China and Mongolia and moderately common in Korea and Japan (see Figure 27). However, there is considerable variation across registries and Hong Kong has high incidences. With the exception of this registry, rates are generally increasing (see Figure 28).

One problem is that there are various subtypes and these have differences in risk factors (Sagae et al., 2003). In Japan, clear cell lesions may be more prevalent than elsewhere (see Table 8). One study in low incidence Taiwan showed marked differences in the distribution of histologic subtypes compared with high-incidence populations (Yen et al., 2003). Nevertheless there is an overall link with exposure to estrogen, and full-term and incomplete pregnancies, lactation, and oral contraceptive use are protective (Zhang et al., 2004a; 2004c). Although a CYP1A1 polymorphism was not related to ovarian malignancies in one Japanese study (Sugawara et al., 2003), intake of soy and isoflavones is inversely related to risk (Zhang et al., 2004d; Sakauchi et al., 2007), while hormone replacement therapy increases the chances of developing an ovarian cancer (Zhou et al., 2008).

Overweight is a factor in Japanese (Niwa et al., 2005), especially with change of BMI after 20 years of age (Hirose et al., 1999). The situation 5 years before diagnosis appears important in Chinese (Zhang et al., 2005). Sedentary behaviour also elevates the risk (Zheng et al., 1993; Zhang et al., 2004e), decline being observed with increasing duration of strenuous sports and frequency of activity-induced sweating among pre-menopausal women, and moderate post-menopausal activity (Zhang et al., 2003).

Consumption of foods low in fat but high in fibre,
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The most important risk factors appear to be estrogen exposure related, including early age at menarche, late age at menopause and nulliparity (Xu et al., 2004; Wernli et al., 2006), while pregnancies, including induced abortion, generally reduce the risk (Xu et al., 2004). Oral contraceptive and IUD use also protect against endometrial cancer (Tao et al., 2006). Breastfeeding may reduce (Okamura et al., 2006) while long-term tamoxifen and ever-use of sex hormones may promote the development of lesions in Japanese women (Khan et al., 2006; Yamazawa et al., 2006). Findings for polymorphisms in hormone metabolizing, receptor and sex hormone-binding globulin genes are also in line with an estrogen exposure etiology (Iwamoto et al., 2003; Kataoka et al., 2007; Tao et al., 2006; 2007) and soy foods may be protective (Xu et al., 2004b; 2007a). However, pregnancy history, menopause age, BMI and presence of diabetes mellitus or hypertension were not related to endometrial tumour development in one study (Nakamura et al., 2006).

Hormone involvement is also suggested by a positive link with adult but perhaps not adolescent obesity (Shi et al., 1993b; Xu et al., 2002; Wen et al., 2008). In particular, upper-body fat deposition is associated with an increased risk of endometrial cancer (Xu et al., 2005) and adult weight gain, especially during the peri-menopausal period, should be avoided (Xu et al., 2006b). Obesity-related insulin resistance and proinflammatory effects may play important roles (Wen et al., 2008) and both lower intensity lifestyle activities like walking and doing household chores and intentional exercise can reduce endometrial cancer risk (Matthews et al., 2005). Those with sedentary jobs or reporting sedentary life-styles were earlier found to have a somewhat increased risk (Shi et al., 1993a).

Diets rich in animal fat and animal protein may play an important role in the etiology of endometrial cancer. (Shi et al., 1993b; Xu et al., 2006a), while protection is afforded by dietary fiber, retinol, beta-carotene, vitamin C, vitamin E and vitamin supplementation (Xu et al., 2007b), with positive contributions for dark green/dark yellow vegetables, fresh legumes, and allium vegetables but not fruit (Tao et al., 2005). Polate intake is beneficial, interacting with MTHFR polymorphisms (Xu et al., 2007; 2008). Coffee consumption is also reported to protect against endometrial cancer in general (Hirose et al., 2007; Shimazu et al., 2008), as well as the endometrioid adenocarcinoma in postmenopausal women (Koizumi et al., 2008). Tea consumption demonstrated an inverse association in one study (Xu et al., 2007a). Paradoxically, cigarette smoking and alcohol may also significantly reduce the risk of endometrial cancer (Hosono et al., 2008; Zhou et al., 2008).

A pointer to toxic agent effects was provided by the reported link with textile industry exposure in Shanghai (Wernli et al., 2008) but expression of s major DNA repair protein was found to be without effect in Korea (Jo et al., 2007).

Cervix uteri

The incidence of cervical cancer is generally low in China, moderate in Japan and somewhat higher in Korea and Mongolia (see Figure 31). Rates are generally decreasing (see Figure 32), with some exceptions like in the elderly in Korea (Jo et al., 2007), this also being observed for mortality (Shin et al., 2008). However, it remains an important health problem among women in both China and Mongolia (Shi et al., 2008), Taiwan and Hong Kong (Tay et al., 2008) and Korea and Japan (Konso
et al., 2008). In Taiwan, interest focused in the 90’s on an increasing trend in recent cohorts (birth after 1963) with a possible role of female sex hormones as an age effect, promiscuous sexual activity as a period effect and change in reproductive behavior as a cohort effect (Wang and Lin, 1996; 1997). The ratios of SCC to AC are shown in Table 9 for selected registries. Typically, adenocarcinomas account for 15-20% of the total burden.

The major risk factor is well recognized to be exposure to high-risk human papilloma virus (HPV) strains. The prevalence of high risk forms of the virus in Asian populations is well documented (Ghim et al., 2002; Shin et al., 2003). Levels in Shanghai are now the same as the worldwide rate, viral load predicting cervical lesions overall (Zhang et al., 2008). Both cervical cancer and cervical intraepithelial neoplasias (CIN) are highly influenced by HR-HPV viral load (Zhao et al., 2004). Seroprevalence correlates with genital HPV exposure in young Korean women, but its meaning in young men is unclear (Clifford et al., 2007). HPV status and histologic grade are independent predictive risk factors for progression and may be useful in the management of CIN (Konno et al., 1998).

Rate of high-risk HPV ranges from about one third in Hong Kong (2007) and lifetime ETS exposure is a major determinant in Japan (Yoshikawa et al., 1999). In Mongolia, lifetime number of sexual partners and induced abortions were shown to be directly associated with HPV DNA and/or seroprevalence (Dondog et al., 2008) and sexually transmitted infections are common, being found in 53% of female attendees of an urban STD clinic (Garland et al., 2001).

Smoking is a well established risk factor (Hirose et al., 1996; 1998; Matsumoto et al., 2003; Odongua et al., 2007) and lifetime ETS exposure is a major determinant for contracting cervical neoplasms among nonsmoking women in Taiwan (Wu et al., 2003). Chlamydia trachomatis infection were revealed may also be a significant risk factor for CIN (Matsumoto et al., 2003). Diet is also an important influence and daily intake of fruit and frequent consumption of boiled or broiled fish are protective (Hirose et al., 1996; 1998)

Health services clearly need to emphasize education about cervical cancer prevention while concentrating on screening (Woo et al., 2005; Jo et al., 2007; Jun et al., 2009). In Taiwan, with about 50% compliance with
screening guidelines, cancer knowledge is the most significant factor determining attendance (Liao et al., 2006). In China’s rural areas with low-resource settings visual inspection with Lugol’s iodine can be one of the primary screening tests if the screening frequency is to be increased (Li et al., 2006). HPV testing is another alternative and in Japan, sensitivity and the positive predictive value for detecting CIN proved superior to cytology in one investigation (Inoue et al., 2006). Based on comparisons of HPV testing and Pap with the existing healthcare infrastructure in China, however, it was concluded that refinement of primary HPV screening using centralized labs is needed (Belinson et al., 2001).

For the future the great long term hope is being placed on vaccination, although there remain barriers other than simply high monetary cost, including uncertain length of vaccine effectiveness, low perceived risk of HPV infection, no immediate perceived need of vaccination, anticipated family disapproval and fear of the pain of injection (Kwan et al., 2008). It has been estimated that the vaccine is cost-effective; for it to be affordable, however, even with financing assistance, vaccine prices may need to be even lower (Goldie et al., 2008).

Brain and Nervous Tissue Cancer

Brain and nervous tissue cancers appear to be more prevalent in China and Korea than in Japan and Mongolia (see Figure 33). There does not appear to be any consistent trend over time, at least in the last 20 years (see Figure 34), although this might depend on the type and sex (Kaneko et al., 2002).

Risk of brain cancer increases with consumption of salted vegetables and salted fish (Guo et al., 1994; Hu et al., 1998; 1999a), as well as liquor intake and diseases related to the brain (Hu et al., 1998), while vegetables and fruit intake of vitamin E calcium may be protective (Hu et al., 1998). Employment in textile industry maintenance jobs and exposure to wool products may be associated with an increased risk of brain tumors (Gold et al., 2008) and meningiomas were found to be positively associated with occupational exposure to lead, tin, cadmium and ionising radiation (Hu et al., 1999b). Patients with NAT2*7 alleles tend to have high-grade astrocytomas or glioblastoma multiforme (Liu et al., 2008). In Korea, significant increase in age-standardized rate ratios of cancers for high-power vs. low-power sites, with the exceptions of total cancer and of brain cancer in women (Ha et al., 2003). Recently, no effects were established for mobile phone use and exposure to radio frequency electromagnetic fields (Takebayashi et al., 2008).

Thyroid cancer

Thyroid cancer is of medium importance in Japan and Korea, but is rarer in China and Mongolia (see Figure 35), but appears to be on the increase (see Figure 36). This is in line with increasing obesity since body size in early life...
as well as in adult is associated with an increased risk of papillary thyroid cancer (Oh et al., 2005; Suzuki et al., 2008). Despite the female predominance, there do not appear to be clear associations with reproductive factors (Wong et al., 2006). A history of goiter/nodules, CT examinations, and familial cancer are risk factors, while smoking and alcohol drinking, as well as tea consumption, may be protective (Zhe et al., 2006; Nagano et al., 2007).

**Non-Hodgkins Lymphomas and Leukemias**

Non-Hodgkins lymphomas (NHL) are more prevalent in Japan and Korea than China and Mongolia, in that order (see Figure 37), and are generally increasing in incidence (see Figure 38), while leukemias are moderately frequent throughout the region (see Figure 39), but possibly decreasing (see Figure 40).

The distribution of NHL subtypes may also be changing, as evidenced in Taiwan (Chang et al., 2008), and risk factors include HBV or HCV infection (Ohsawa et al., 1999; Kim et al., 2002; Matsuo et al., 2004c), with influence for polymorphisms in folate-metabolizing genes (Hishida et al., 2003; Matsuo et al., 2004a) and p53 (Hishida et al., 2004). DNA repair may play a limited role in lymphomagenesis independent of the histological subtype (Matsuo et al., 2004), while regular alcohol consumption is associated with reduced risk, with no change observed for smoking (Matsuo et al., 2001).

With leukemia, environmental pollution with rare-earth elements and organophosphorus pesticides may be important (Wu et al., 2003) as well as working exposure to benzene, synthetic fiber dust, radioactive materials, and toluene (Adegoke et al., 2003). Possible protective effects of green tea intake have been reported (Wu et al., 2003; Zhang et al., 2008). While higher mortality rates for leukemia were noted in some age groups in areas near AM radio broadcasting towers (Park et al., 2004), findings in Japan do not support any leukaemogenic impact of nuclear power plants (Yoshimoto et al., 2004)

**Childhood cancers**

Data on time trends are very limited and surveys do not appear to have been conducted recently (Ajiki et al., 1994). Paternal preconception smoking is related to a significantly elevated risk of childhood cancers, particularly acute leukemia and lymphoma (Ji et al., 1997; Liu et al., 1997), with possible modification by the CYP1A1 genotype (Lee et al., 2009). Maternal exposure to organic solvents during periconception might also be important (Sung et al., 2007) and DNA repair may exert an influence (Wang et al., 2006). There is also some evidence for leukemia risk increase associated with residential proximity to high-voltage power (Mizoue et al., 2004) or AM radio transmitters (Kim et al., 2002), and high MF exposure (Kabuto et al., 2006). Furthermore, childhood brain tumors are associated with paternal use of hard liquor prior to the pregnancy (Hu et al., 2000).
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Future Perspectives

From the present overview, it is clear that a great deal of information has already been generated regarding cancer prevalence and risk factors in North-East Asia, as stressed earlier in a recent review (Park et al., 2008). The various collaborative efforts within countries, like the Japan Collaborative Cohort Study (Tamakoshi, 2007), the Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan, the Korean Multicenter Cancer Cohort Study including a Biological Materials Bank (KMCC-1) (Yoo et al., 2002) and other cohorts in Korea (Yoo et al., 2005) and elsewhere will guarantee that new information will continue to be produced. The focus will continue to be on genetics-environment interactions as at the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (Tajima et al., 2000; Hamajima et al., 2001). Genotype-phenotype links will also be stressed (Shin et al., 2008).

It is to be hoped that the collaboration started between China, Korea and Japan with the Japanese-Korea-China (KOJAC) (Tajima et al., 2009) study will expand in the future so that the common goals of cancer control in the region can be realised. The new international research groups set up under the auspices of the Japanese Ministry of Health, Labour and Welfare should contribute to this aim.

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