Original Article

Frequent occurrence of gastric cancer in Asian kindreds with Li–Fraumeni syndrome


Type of cancer and age of onset in individuals with inherited aberrations in the tumour suppressor gene TP53 are variable, possibly influenced by genetic modifiers and different environmental exposure. Since 2009, the modified Chompret criteria (MCC) have been used to identify individuals for TP53 mutation screening. Using the TP53 mutation database maintained by the International Agency for Research on Cancer (IARC), we investigated if the MCC, mainly developed for a Caucasian population, was also applicable in Asia. We identified several differences in Asian families compared with similar Caucasian cohorts, suggesting that identification and management of Li–Fraumeni syndrome in Asia do not completely mirror that of North America and Western Europe. Early gastric cancer (<40 years) may be considered a new addition to the MCC especially for Asian families.

Conflict of interest
The authors declare no conflicts of interest.

Li–Fraumeni syndrome (LFS, OMIM 151623) is an autosomal dominant cancer predisposition syndrome associated with clustering of early-onset cancers of the central nervous system, sarcomas and pre-menopausal breast cancer (1). Germline mutations in the tumour suppressor gene TP53 is the only known genetic defect underlying LFS/Li–Fraumeni-like syndrome (LFL), accounting for 20–70% of families matching clinical definitions of LFS/LFL, respectively (2). Currently, the ‘modified Chompret criteria’ (MCC) is used to identify probands for TP53 mutation testing, a practice which identifies mutations in 21–29% of referred probands (3, 4).

Candidates for TP53 mutation testing include (i) proband with a tumour of the narrow LFS spectrum [soft-tissue sarcoma, osteosarcoma, brain tumour, adrenocortical carcinoma (ACC), breast cancer] before 36 years or with any childhood solid tumour, within a family containing at least one first-degree or second-degree relative with a tumour of the LFS spectrum (except breast cancer if the proband has a breast cancer) under 46 years; (ii) patients with multiple primary tumours (except breast cancers), two of which belong to the LFS spectrum, the first developing before age 46 years; and (iii) patients with ACC or choroid plexus carcinoma or papilloma before the age
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of 15 years, or rhabdomyosarcoma before the age of 5 years (5).

Wide variation in the site and age of cancer onset in LFS/LFL individuals may be attributed to mutation-specific effects (6), gene–gene interactions, epigenetic or environmental factors. This phenotypic heterogeneity makes it difficult to predict cancer risk accurately for TP53 mutation carriers. Currently, LFS/LFL management involves comprehensive regular screening from a young age (7) which may improve survival (8), although the issue of managing asymptomatic germline TP53 mutation carriers remains controversial (1, 8).

Comprehensive screening protocols are not economically feasible in resource-limited areas such as Asia. Thus, screening recommendations should consider geographic differences in cancer prevalence to better stratify resources towards the most beneficial imaging or laboratory tests.

The vast majority (83.6%) of data from the International Agency for Research on Cancer (IARC), the largest data repository for TP53 mutation carriers, originate from Western Europe (n = 101) and Northern America (n = 113), mostly of Caucasian origin. Despite Asia being the most populous continent, inhabited by 60% of the world’s population, knowledge on LFS/LFL incidence in this region remains poor. Population risk of several cancer types differ between Caucasians and Asians, suggesting that the relative risk associated with TP53 alterations may also differ. In this study, we examined tumour patterns of individuals with LFS and/or inherited TP53 mutations to identify differences between Asian and Caucasian carriers.

Methods

Data on LFS/LFL cases was obtained from the TP53 Database managed by IARC (http://p53.iarc.fr_version R16, November 2012) and three previously unreported Malaysian families. These data are attached in Supporting Information.

Countries studied are situated in East and South-East Asia (thereafter, referred to as ‘East Asia’) and include China, Taiwan, Japan, Korea, Malaysia and Singapore. As other countries from this region e.g. Thailand, Vietnam and Indonesia do not have any cases reported in the IARC database, it was assumed that findings from these six countries, which encompass over 70% of the East/South-East Asian population, are representative of the region. Pedigrees and available epidemiological data were reviewed, noting age of subjects, types of cancer and types of TP53 mutation. Similar analyses were done for North America and Western Europe.

Demographic and clinical characteristics of all subjects were summarized using descriptive statistics. The $\chi^2$ test was used to compare differences between Asian and non-Asian populations in (i) mutation distribution in known TP53 mutation hotspots; (ii) tumour incidence; and (iii) frequency of individual cancer types. The parametric independent samples t-test was then used to compare mean age of gastric cancer development between the cohorts, which were considered to be normally distributed. Results were considered statistically significant if the two-sided p < 0.05.

Results

East Asia TP53 mutation patterns

One hundred fifty-nine subjects from 42 families with LFS/LFL or TP53 mutation from East Asia were analysed. Mutations were found in all exons except exons 2, 9 and 11. Similar to the non-Asian cohorts, most mutations occur in the gene region encoding the DNA-binding domain (DBD) of TP53 (90.3% and 84.6%, respectively). There are six frequently mutated hotspots (9) with no significant difference in the distribution of mutations between the Asian and non-Asian populations (p = 0.35) (Fig. 1).

Tumour accrual with age

One hundred thirty-eight of the 159 of our East Asian subjects were affected by cancer, with accrual rates of cancer incidence shown in Fig. 2. Before age 35, 50% of LFS/LFL individuals presented with cancer in each of the three cohorts. Beyond this age, however, divergence was observed with the Asian cohort, although the accrual trends of Americans and Europeans remained similar. By age 50, 90% of Asian TP53 mutation carriers had developed cancer, compared with 82% of Americans and 80% of Europeans. This excess of cancers reported in Asians aged 35–50 is the most apparent difference observed.

LFS tumour patterns

Breast cancer (28.1%) and stomach cancer (15.8%) were the most frequently observed cancers among Asian TP53 mutation carriers. Given the excess of cancers seen in Asian carriers aged between 35 and 50, we examined the tumour spectrum in these cohorts (Table 1). There was no significant difference in the incidence of LFS-associated cancers (p = 0.40), suggesting that the distinction between Asian patients with LFS and their non-Asian counterparts was due to cancers outside of this spectrum.

Gastric cancer was the only tumour type in which a significant difference was observed (15.65% in Asians, 0.99% in North Americans and 3.59% in Europeans, p = 0.00). Additionally, the average age of presentation was younger in East Asians (39 compared with 46 years, p = 0.10). While not achieving statistical significance, there are notably more cases of young gastric cancer in the Asian cohort with three diagnoses made at age 20 while the youngest gastric cancer patient in either Caucasian cohort was 29 years. Thirteen (56%) of the Asian gastric cancer patients were diagnosed before the age of 40 while there were only two such subjects in both non-Asian datasets combined.

Gastric cancer in East Asia

GLOBOCAN 2008 reports gastric cancer as one of the most common cancer types in South-East Asia, with an estimated age-standardised rate (ASR) of 24.2 compared
Fig. 1. Comparison of mutation frequency at each codon for Asians (top), North Americans (middle) and Western Europeans (bottom).
Table 1. Distribution by tumour type for the three geographical regions

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Numbers (%) of first cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Asia</td>
</tr>
<tr>
<td>LFS spectrum</td>
<td></td>
</tr>
<tr>
<td>Adrenal carcinoma ≤15 years</td>
<td>64</td>
</tr>
<tr>
<td>Soft tissue sarcoma ≤36 years</td>
<td>11</td>
</tr>
<tr>
<td>Breast cancer ≤36 years</td>
<td>22</td>
</tr>
<tr>
<td>Brain tumour ≤36 years</td>
<td>14</td>
</tr>
<tr>
<td>Osteosarcoma ≤36 years</td>
<td>8</td>
</tr>
<tr>
<td>Total LFS spectrum</td>
<td>64</td>
</tr>
<tr>
<td>Non-LFS spectrum</td>
<td></td>
</tr>
<tr>
<td>Adrenocortical carcinoma &gt;15 years</td>
<td>64</td>
</tr>
<tr>
<td>Soft tissue sarcoma &gt;36 years</td>
<td>11</td>
</tr>
<tr>
<td>Breast cancer &gt;36 years</td>
<td>16</td>
</tr>
<tr>
<td>Brain tumour &gt;36 years</td>
<td>3</td>
</tr>
<tr>
<td>Osteosarcoma &gt;36 years</td>
<td>2</td>
</tr>
<tr>
<td>Bronchus/lung cancer</td>
<td>4</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>4</td>
</tr>
<tr>
<td>Leukaemia/lymphoma</td>
<td>5</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>1</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>2</td>
</tr>
<tr>
<td>Skin cancer (excluding melanoma)</td>
<td>0</td>
</tr>
<tr>
<td>Stomach cancer</td>
<td>22</td>
</tr>
<tr>
<td>Uterine cancer</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>139</td>
</tr>
</tbody>
</table>

LFS, Li–Fraumeni syndrome.

with 6.3 and 4.0 in Western Europe and North America, respectively (both genders). To observe if the apparent excess of gastric cancer in Asian TP53 mutation carriers is proportional to the increase in the general population, we compared the frequency of gastric cancer with that of colorectal cancer (CRC), which has been associated with inherited TP53 mutation in European and Northern American LFS/LFL families (10).

Based on population incidence estimates from GLOBOCAN, the ratio of gastric cancer to CRC is 0.76 and 0.17 in East Asian and Northern American/Western European populations, respectively. These estimates suggest that, adjusted to CRC, gastric cancer is 4.47 times more frequent in Eastern Asian than in the Northern American/Western European populations. However, in Asian TP53 mutation carriers, the incidence of gastric cancer is 8.94 times more frequent for every case of CRC compared with those from the Caucasian cohort. These estimates suggest that the increased incidence of gastric cancer in Asian TP53 mutation carriers cannot be solely attributed to increased population risk. Nevertheless, these estimates are based on small numbers and should be interpreted cautiously.

Discussion

Based on the de novo TP53 mutation rate of 1:5000 to 1:20,000 births (11, 12), 1500 to 6200 new TP53 mutations should occur in the East Asian region.
each year. Yet, only 42 East Asian LFS/LFL families have been identified to date, highlighting the under-recognition of this condition. MCC recommendations for TP53 mutation screening are associated with high sensitivity and predictive value (4, 12), but these criteria and their subsequent modifications are largely based on LFS/LFL patterns observed in Caucasian families. Given the phenotypic heterogeneity associated with LFS/LFL, ethnic and geographic background may play a defining role.

Multiple genetic traits distinguish Asian and Caucasian populations, yet tumour patterns of Asian TP53 mutation carriers are similar to that of Northern American/Western European carriers, especially for core MCC cancer types (Table 1). This suggests that the MCC captures a group of patients with extraordinarily similar forms of cancer predisposition, independently of ethnic and geographic variation. Furthermore, cancer accrual with age appears identical until the age of 35, corresponding to the ‘cut-off’ age used in the MCC to define most cancers of the narrow LFS spectrum.

Beyond this age, a more rapid cancer accrual is seen in Asians compared with North Americans and Western Europeans. This is caused by an excess of gastric cancers in Asian LFS/LFL families as the frequency of other cancer types remain similar. This statistically significant difference in gastric cancer incidence suggests a possible association with TP53 mutation carriage in Asians. Additionally, gastric cancer occurs on average 10 years earlier in Asian than in Caucasian carriers, with over 15% of cases diagnosed before age 30.

Gastric cancer incidence is approximately five times higher in the general population of Eastern Asia compared with Western populations. This has been suggested to be due to a combination of dietary (high salt diet), environmental (chronic Helicobacter pylori infection) and genetic susceptibility risk factors. Thus, gastric cancer cases in Asian TP53 mutation carriers might phenocopy the frequent occurrence of this cancer in the general population. In recent years, the same question was raised for the frequent occurrence of early CRC in TP53 mutation carriers in Europe and in Northern America. While the actual excess risk of CRC in TP53 mutation carriers is not precisely known, it was concluded that risk of early CRC risk should be considered in the clinical management and follow-up of LFS/LFL (13). Notably, the frequency of CRC in Asian TP53 mutation carriers is comparable to North American/Western European series. When adjusted to the frequency of CRC, the excess occurrence of gastric cancer in Asian TP53 carriers was about two times higher than estimated if this cancer was occurring at a rate proportional to its occurrence in the general population. We, therefore, suggest that early gastric cancer may represent a specific feature of the tumour pattern in Asian LFS/LFL families.

Approximately 90% of young gastric cancer patients lack a family history of gastric cancer. Milne et al. suggest that early gastric cancers are caused by a predisposing genotype that facilitates cancer development following various environmental triggers (14). TP53 mutations could represent a candidate mutation which facilitates cancer development and triggers early development of this usually late onset cancer in high-risk populations such as in East Asians.

One notable environmental difference between Caucasian and Asian populations is the higher seroprevalence of H. pylori in the latter. While common exposure to H. pylori may explain some cases of familial gastric cancer, only a small percentage of infected individuals eventually develop gastric cancer. Additionally, in recent years, there has been a reported decrease in incidence of sporadic gastric cancer in older patients, indicating that measures to remove environmental risk factors may be effective. Yet, early onset gastric cancer in cases of familial clustering has remained stable, suggesting instead a role of genetic variants (15). Therefore, instead of purely caused by phenocopies, TP53 mutation carriers may be oversensitive to risk factors which also contribute to increased incidence of gastric cancer in the general population.

Several hypotheses which are not mutually exclusive may explain the excess of gastric cancer incidence in Asian TP53 mutation carriers. These include (i) susceptibility-associated genetic traits may be particularly common in Asian populations and synergise with reduced p53 function to increase gastric cancer risk; and (ii) p53 may govern protective responses against potentially carcinogenic effects of environmental risk factors.

Recent studies in Han Chinese populations have identified polymorphisms in candidate genes which potentially influence gastric cancer risk. Interestingly, several are involved in DNA repair, including XRCC1 (X-ray repair cross-complementing group 1; variants c.910A>G and c.1804C>A) (16) and ERCC4 (excision repair cross-complementing group 4; variant rs744154) (17). Another susceptibility locus for gastric cancer is MLL3 (mixed lineage leukaemia 3; variants rs6943984 and rs4725443). The MLL3 protein interacts with ASC-2, a multifunctional coactivator, forming the ASC-2 complex (ASCOM) which interacts directly with p53 and is required for p53-target genes to respond to DNA damage (18, 19). Also, the G/G variant in rs2076167 of the gene encoding peroxisome proliferator-activated receptor (PPAR) has been associated with increased risk of gastric cancer in a recessive model through a case–control study carried out in Jiangsu, China. This association shows significant gene–environment interaction as the incidence of gastric cancer in G/G individuals was particularly strong among those who reported a high salt diet (20).

Ethnicity data are not recorded in the IARC database, therefore we have based our conclusions on the premise that the populations studied are relatively homogenous, with the Asian cohort largely made up of Indochinese/Malay ethnic subjects while the Western cohorts are of Caucasian ethnicity. Additionally, issues of ascertainment bias may happen in Asia with under-reporting of cancer incidence and lack of TP53 mutation-screening facilities.

Notwithstanding these limitations, we demonstrate that tumour patterns in Asian are very similar to
Caucasian carriers of germline TP53 mutations, despite well-documented differences in genetic makeup, cancer risk factors and cancer incidence. This emphasizes that germline TP53 mutations are the driver mechanism for cancer development rather than facilitating factors that modulate the carcinogenic effects of other environmental or genetic risk factors. Yet, notable differences remain in tumour patterns between Asian and Caucasian LFS/LFL cohorts, and the disparity in resources available for screening asymptomatic germline TP53 mutation carriers further heightens the need to identify and utilize these differences to maximize clinical benefits of local screening programmes.

We speculate that single nucleotide polymorphisms (SNPs) as opposed to diet and environment are the most important factor. Therefore, Asian LFS/LFL individuals remain at increased gastric cancer risk despite migration to the West and an adoption of Western-styled diets. This result has clinical implications on the handling of LFS/LFL families of Asian origin in all geographical regions.

In conclusion, we have shown that gastric cancer is significantly more frequent in Asian TP53 mutation carriers than in Caucasians, highlighting that the ‘one size fits all’ MCC may not be universally appropriate and should perhaps be adapted to geographic and population context. It remains to be evaluated whether there is a benefit in screening for gastric cancer in Asian TP53 mutation carriers.

Supporting Information

Additional supporting information may be found in the online version of this article at the publisher’s web-site.

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References