Population-based differences in treatment outcome following anticancer drug therapies

Brigette B Y Ma, Edwin P Hui, Tony S K Mok

Population-based differences in toxicity and clinical outcome following treatment with anticancer drugs have an important effect on oncology practice and drug development. These differences arise from complex interactions between biological and environmental factors, which include genetic diversity affecting drug metabolism and the expression of drug targets, variations in tumour biology and host physiology, socioeconomic disparities, and regional preferences in treatment standards. Some well-known examples include the high prevalence of activating epidermal growth factor receptor (EGFR) mutations in pulmonary adenocarcinoma among northeast (China, Japan, Korea) and parts of southeast Asia (excluding India) non-smokers, which predict sensitivity to EGFR kinase inhibitors, and the sharp contrast between Japan and the west in the management and survival outcome of gastric cancer. This review is a critical overview of population-based differences in the four most prevalent cancers in the world: lung, breast, colorectal, and stomach cancer. Particular attention is given to the clinical relevance of such knowledge in terms of the individualisation of drug therapy and in the design of clinical trials.

Introduction

It has long been recognised that different populations have different treatment outcomes following anticancer drug therapy (figure). These disparities often manifest as characteristic patterns of epidemiology, treatment outcome, drug response, and toxicities that are clustered among specific ethnic groups or geographical regions. It has long been thought that such differences exist as a result of complex interactions between biological and environmental factors, but it was not until the Human Genome Project and advances in molecular biology that some of these biological factors have gradually come to light. There is now an expanding body of work that describes differences between ethnic groups in the distribution of genetic polymorphisms that affect DNA-repair enzymes, drug-metabolising enzymes, and cellular transporters of cytotoxic chemotherapy. These genetic variants are often single nucleotide polymorphisms (SNPs) and haplotypes (combinations of SNPs that are inherited together), which can be phenotypically associated with altered enzymatic activity and pharmacokinetics of anticancer drugs. Inter-ethnic variability also extends to the expression of drug targets and receptors that are relevant to predicting the efficacy of target-based drugs. It is therefore timely to review these new findings in light of their relevance to the contemporary practice of oncology and the development of new anticancer drugs.

The aim of this review is to explore the biological and environmental bases of population-based differences in tumour biology and treatment outcome following cytotoxic chemotherapy and target-based drugs. Biological factors will be discussed in the context of genomic (inherited or acquired) and molecular factors, while environmental factors will be discussed in terms of disparities in access to health-care resources, public health policy, and treatment standards. The term “population” used in this Review refers to people of different sex, ethnic origin, or those living in certain geographical regions within a country or across different continents. This review is limited to the four most prevalent cancers in the world—lung, breast, colorectal, and gastric cancers—and will focus only on sporadic cancers: therefore excluding hereditary cancer syndromes.

Lung cancer

Lung cancer accounts for over 1·3 million deaths per year worldwide, and continues to be the most prevalent and one of the most fatal malignancies.1 Epidemiological studies have projected a decline in the incidence of lung cancer in the UK and USA, while an increase is expected in China.2 Ethnic origin and sex have been assessed as possible predisposing factors for lung cancer, and it has been estimated that Asian Americans (Americans of Chinese, Korean, or Japanese background or heritage) have a four-fold higher risk of lung cancer than white
Biological and genetic differences in drug responses and susceptibility to cancer
By far the most striking difference in the distribution of genetic mutations in lung cancer is the high prevalence of somatic mutations of the epidermal growth factor receptor (EGFR) among Chinese, Korean, and Japanese female non-smokers with lung adenocarcinoma. The mutational sites are clustered between exons 18 and 21 of the EGFR gene, in the tyrosine kinase binding domain. Patients with lung cancers that harbour base-pair deletions at exon 19 and the L858R mutation at exon 21 respond very well to EGFR tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib. In addition to being a powerful predictive biomarker of response to EGFR TKIs, activating EGFR mutations also predict better clinical outcome after gefitinib therapy. In the IPASS study, 1,217 patients from China, Hong Kong, Taiwan, Japan, Thailand, Indonesia, Phillipines, Singapore, and Malaysia were randomly assigned to either gefitinib alone (n=609) or carboplatin–paclitaxel (n=608) for the first-line treatment of incurable lung adenocarcinoma. The gefitinib group had longer survival of 24 months and an overall response rate of 73%. This result is impressive considering that historically, unselected patients with lung cancers have a median overall survival of just 8 months and a response rate of 20% when treated with first-line platinum-based chemotherapy.

Given the powerful predictive and prognostic effect of EGFR mutational status, it is now necessary to include this factor when deciding on the use of EGFR TKIs in the first-line setting, and in the design of any multi-national clinical trials of lung cancer. Moreover, when analysing survival in a comparative study for lung cancer, the data should be adjusted for any imbalances that arise from the proportion of patients with EGFR mutations, and from the salvage use of EGFR TKIs following study withdrawal, as these factors will strongly affect treatment outcome.

Differences in susceptibility to toxicities of cytotoxic chemotherapy
Differences exist between populations of different ethnic origins in terms of their response and incidence of toxicity to cytotoxic chemotherapy such as taxanes. Sekine and colleagues reported a higher incidence of neutropenia and neutropenic fever among Japanese than US patients who were treated with platinum and taxane combinations. In another study in which Asians (primarily of Chinese descent) and Australians of European ancestry were treated similarly with docetaxel (75 mg/m²) and carboplatin (area-under-the-curve [AUC] of 6), Asian patients experienced a higher incidence of myelo-toxicities and higher response rates (65% vs 31%) than Australians of European ancestry. Such differences in drug efficacy and toxicity might be related to variations in genes involved in the metabolism and transport of docetaxel, such as CYP3A4 and MDRI (also known as ABCB1). For these reasons, some Japanese investigators favour the use of taxanes at lower doses or on a weekly schedule instead of the 3-weekly dosing regimen used in studies of North American and European patients when designing clinical trials for non-small cell lung cancer.

Breast cancer
Breast cancer is the second most common cancer worldwide, and its incidence is rising in east Asia. In multiethnic US populations, the rising incidence of breast cancer is mainly accounted for by increased incidence in white Americans, while the mortality rates of African Americans are 37% higher than white and Asian (Chinese, Korean, Japanese) Americans. This poorer outcome might be due in part to population-based disparities in tumour biology, as some ethnic groups seem to be predisposed to tumours with poor prognostic features, such as high tumour grade, HER2 (also known as ERBB2) overexpression, absent hormone-receptor expression, and the basal-like subtypes known as triple-negative (hormone-receptor negative and HER2
negative) breast cancers. This applies especially to Hispanic and African Americans, even when socio-economic factors have been taken into consideration. For instance, the prevalence of triple-negative breast cancer was reportedly 39% in premenopausal African Americans, compared with 8% in the equivalent Japanese population.

**Differences in tolerability and response to hormonal therapy**

The CYP450 family of enzymes, including carbonyl reductases and sulotransferases, have crucial roles in the metabolism of anticancer drugs. Inter-ethnic variability in the activity of these enzymes has long been recognised, and has been attributed to some functional polymorphisms in patients with breast cancer. For instance, polymorphic variants of CYP2D6 and SULT1A1 (sulotransferase IAI) have been associated with altered pharmacokinetics and clinical efficacy of selective oestrogen-receptor modulators (SERMs) in some ethnic groups. Variants in the CYP2D6 allele (eg, CYP2D6*4, CYP2D6*5, CYP2D6*10, and CYP2D6*41) and SULT1A1*2 have been linked with the impaired formation of active metabolites of tamoxifen, and therefore contribute to the poorer survival of carriers of such variants who were treated with tamoxifen in the adjuvant and palliative settings compared with non-carriers. The Japanese have a higher prevalence of a SNP in the CYP2D6*10 allele, which is correlated with higher recurrence rates after treatment with adjuvant tamoxifen. By contrast, CYP2C19*17 variants have been associated with higher enzymatic activity and possibly better survival. Punglia and colleagues addressed the clinical significance of CYP2D6 polymorphisms by investigating the effect of genotype variants on the survival of patients treated with adjuvant tamoxifen versus aromatase inhibitors in two multicentre phase 3 trials. Although these phase 3 studies found that aromatase inhibitors improved disease-free survival compared with tamoxifen, Punglia and colleagues did not find any differences in survival among patients treated with either drug who were carriers of wild-type CYP2D6. Collectively, these studies suggest that CYP2D6 genotyping as a tool for individualising endocrine therapy in patients with breast cancer should be further prospectively evaluated.

**Differences in tolerability and response to cytotoxic chemotherapy**

Both Chinese and African patients are known to experience a higher incidence of myelotoxicity from adjuvant anthracycline or docetaxel for breast cancer than white patients. For African Americans and African Caribbeans, this susceptibility has been attributed to the generally lower levels of pre-treatment neutrophil (and also platelet) counts compared with white patients, and even among healthy individuals. Chinese patients might be more prone to myelotoxicity because of their lower pharmacokinetic clearance of docetaxel compared with white patients; a trend that has not been noted in African Americans. To explain these differences in pharmacokinetics, researchers have tried to correlate altered drug clearance and exposure (eg, AUC) with the presence of functional variations in genes that encode drug-metabolising enzymes and membrane transporters. To date, such phenotype–genotype associations have been reported in people of Chinese, Malaysian, and Indian ancestry treated with doxorubicin. Polymorphic variants of the PXR*1B haplotype clusters have been linked to reduced activity of the PXR (pregnane X receptor; encoded by the NR1I2 gene), and its downstream target enzymes, CYP3A4 and ABCB1 (also known as MDR1), which resulted in lower clearance of doxorubicin. Furthermore, people of Chinese, Malaysian, and Indian ancestry who carried variants of the multidrug-resistance gene (ABCB1) and the CBR1 D1 (carbonyl reductase 1) gene experienced an increased clearance of doxorubicin and reduced peak plasma levels of doxorubicinol (an active metabolite of doxorubicin). By contrast, SNPs in SLC22A16 (solute carrier family 22) are associated with an increased AUC of doxorubicin and doxorubicinol concentrations, and are more frequent in Chinese than in individuals.

Compared with studies on doxorubicin, studies of the phenotype–genotype association between SNPs and the pharmacokinetics of taxanes have been inconclusive. The presence of SNPs or haplotypes of ABCBI, ABCG2, and CYP2C8 was shown not to be significantly correlated with altered clearance or exposure to paclitaxel (except with some of its metabolites). Similarly, no association was found between docetaxel clearance and variants of genes that encode PXR, hepatic nuclear factor 4a, constitutive androstane receptor, and other CYP450 enzymes.

**Colorectal cancer**

Colorectal cancer is most prevalent in western countries, although the incidence in east Asia is approaching that in the west. Population-based studies from the US have revealed marked disparities in the prognosis of colorectal cancer in populations of different ethnic origin, such that the mortality rate is 45% higher in African Americans than in the white population. By contrast, Asian Americans are more likely to develop smaller and distally located colorectal cancers than African Americans, and tend to survive the disease longer than patients from other ethnic groups. One of the most debated factors that potentially contributes to the poorer outcome noted in African-American patients with colorectal cancer is whether there is a disparity in the receipt of oncological treatment. Although unequal access to the healthcare system was once thought to be a key factor contributing to poor outcome in African-American patients, a large population-based study found that even among medically insured patients who had equal opportunity to
receive advice by medical oncologists on adjuvant chemotherapy, older African Americans were less likely to receive chemotherapy than white Americans, suggesting that other factors such as disease stage and social support might be more important.\(^\text{17}\)

This section will focus on those genomic biomarkers of toxicity and response to anticancer drugs for colorectal cancer that have shown population-based differences. Although recent studies have proven the predictive value of KRAS mutation and response to cetuximab,\(^\text{38}\) and topoisomerase I expression and response to irinotecan and oxaliplatin,\(^\text{39}\) they will not be discussed here since population-based differences have not yet been reported with these biomarkers.

**Variations in tolerance and response to irinotecan**

Irinotecan is commonly used for the treatment of colorectal cancer. In colorectal cancer, variability in tolerance to irinotecan has been well described between populations, and has a pharmacogenomic basis. Uridine diphosphate glucuronosyltransferase (UGT1A1) is responsible for the metabolism of SN38, the active metabolite of irinotecan, and functional variants of the UGT1A1 gene have been associated with reduced activity of this enzyme and altered pharmacokinetics of irinotecan.\(^\text{40}\) These gene variants arise from insertions of varying numbers of TA repeats at the TATA box sequence of the UGT1A1 promoter, resulting in reduced gene transcription. The UGT1A1*28 polymorphism represents the presence of a (TA),TAA sequence in the promoter region, instead of the wild-type (TA),TAA. Carriers can be heterozygote TA(6/7) or homozygote TA(7/7). The UGT1A1*28 allele variants have been the most studied in colorectal cancer, and can be found in 20–50% of white\(^\text{41}\) and Japanese individuals,\(^\text{42}\) respectively, but are less frequent in Chinese (<20%) individuals.\(^\text{43}\)

Retrospective and prospective studies in white and Japanese patients have shown that homozygotes of UGT1A1 TA(7/7) genotype are seven to nine times more likely to experience severe diarrhoea\(^\text{44}\) and neutropenia\(^\text{45}\) than heterozygous TA(6/7) or wild-type TA(6/6) genotypes after treatment with irinotecan.\(^\text{46}\) This might be explained by the observation that patients who are homozygous for UGT1A1 TA(7/7) have a higher AUC of SN38\(^\text{47}\) and lower SN38 glucuronidation rate.\(^\text{48}\) Based on these findings, the US Food and Drug Administration (FDA) updated the drug label of irinotecan by including pharmacogenetic information in 2005. By contrast, the association between UGT1A1 polymorphisms and response to irinotecan is less clear. In a study of 250 white patients with metastatic colorectal cancer, homozygotes of the UGT1A1 TA(7/7) had better response rates to irinotecan-containing regimens than those with wild-type genotypes.\(^\text{49}\) However, this difference was not detected in a study of Chinese patients, in which most patients (79.7%, 102 out of 128 patients) had the wild-type genotype.\(^\text{50}\)

In addition to UGT1A1 polymorphisms, SNPs or haplotypes of other alleles or genes have shown differences in distribution between ethnic groups. SNPs of the UGT1A1*6 allele have been linked to altered SN38 metabolism and risk of neutropenia in Chinese, Malays, and Indians.\(^\text{51}\) The haplotype structure of promoter variants at UGT1A1 and its transcriptional regulator PBREM (phenobarbital-responsive enhancer module gene) is different between white and African-American individuals.\(^\text{52}\) The functional significance of these variants remains to be determined.

**Variations in tolerance and response to fluoropyrimidines**

In a recent pooled analysis of three multinational trials in patients with colorectal cancer, patients from outside the USA (particularly east Asian) reported higher incidence rates of severe toxicity and drug discontinuation than patients from sites in the USA treated with fluorouracil or capcitabine.\(^\text{53}\) In an attempt to explain this disparity, a Japanese study compared the pharmacokinetics of capcitabine and its metabolites between 20 Japanese and 24 white recipients, but failed to find any differences.\(^\text{54}\)

Other researchers have focused their attention on the inter-ethnic variations in fluorouracil-metabolising genes (eg, dihydropyrimidine dehydrogenase [DPD], encoded by DYPD) and fluorouracil targets (eg, thymidylate synthase). It has been estimated that around 3% of the general global population have partial DPD enzyme deficiency, and might be at risk of developing severe fluorouracil-induced toxicity.\(^\text{55}\) Some of these deficiencies have been attributed to the presence of DYPD point mutations, especially at the DYPD*2 allele,\(^\text{56}\) which can be found in 1% of the general population. However, white patients are more likely to be homozygous (0–9%) carriers\(^\text{57}\) than Japanese or Chinese (<0·2%) patients.\(^\text{58}\) Significant inter-ethnic heterogeneity is also seen in the distribution of other DYPD SNPs and haplotypes;\(^\text{59}\) however, their clinical significance is yet to be determined.

Thymidylate synthase is the inhibitory target of fluorouracil, and a meta-analysis showed that increased thymidylate synthase expression is a negative prognostic factor in patients with advanced colorectal cancer.\(^\text{60}\)

Thymidylate synthase polymorphisms arising from allelic repeats at the promoter enhancer region (TSER) and the 3’-untranslated region (3’-UTR) have been associated with increased toxicity to fluorouracil and capcitabine in a European\(^\text{61}\) and a Korean populations.\(^\text{62}\) The TSER contains a polymorphic tandem repeat sequence (2R or 3R) and a SNP (G>C) within the second repeat of the 3R alleles. The low enzyme expression-related genotypes (2R/2R, 2R/3RC, and 3RC/3RC) are found in 3–32% of Europeans, while the high enzyme expression-related genotypes (2R/3RG, 3RG/3RC, and 3RG/3RG) are found in around 15% of Europeans.\(^\text{63}\) A small Spanish study reported that 49 patients with the low enzyme-expression-related genotypes had a better clinical response to fluorouracil than 40 patients with high enzyme-
expression-related genotypes. Unlike European populations, Chinese and Japanese populations have a much higher prevalence of the triple repeat allele (TSER 3R/3R; 63–67%), but no differences in clinical outcome between genotypes are reported in Japanese patients.

In addition to genomic factors, the question of whether women with Dukes’ stage C colorectal cancer are more likely to benefit from adjuvant fluorouracil than men remains controversial. A subset analysis of a phase 3 study and a retrospective study suggested that women have better clinical outcome following adjuvant fluorouracil-based chemotherapy than men. By contrast, a subset analysis of another phase 3 study found that older men were more likely to benefit from fluorouracil-based chemotherapy, while a large prospective analysis of pooled data from 85,934 patients found no difference in benefit from adjuvant chemotherapy between the different sexes.

Gastric cancer

There are several marked differences in the epidemiology and prognosis of gastric cancer between east Asian (especially Japan) and western populations. The incidence rates of adenocarcinoma of the oesophagus and gastro-oesophageal junction are increasing at a dramatic rate in the west, whereas cancers of the middle distal third of the stomach are more prevalent in Japan. Although the age-standardised incidence rate and crude mortality rates of gastric cancer for all genders in Japan and some western countries have decreased over the past two decades, the reported treatment outcome in Japan is still better than in the west. The 5-year overall survival of resectable gastric cancer is around 70% in specialist Japanese centres, compared with only around 35% in specialist centres in Europe and the UK. The relative contribution of biological versus environmental factors in explaining this disparity in outcome has been a subject of intense debate. Proponents of the theory that tumours in east Asians are less aggressive proposed that this difference had a genetic basis; however, studies published to date have failed to find a genetic difference between clinically comparable gastric cancers in Japan and the west. Population-based studies in North America have had mixed results in terms of ascertaining Asian (Chinese, Japanese, Vietnamese, Fillipino, Korean) ethnic origin as an independent predictor of survival in gastric cancer. A study of over 2000 Asian migrants in Canada found that although Asians were more likely to have proximal gastric cancers, Asian ethnic origin did not predict survival. This contrasts with a study based on the US National Cancer Data Base, which found that Asian ethnic origin, female sex, and distal tumours are among the predictors of better survival in gastric cancer. Female sex has also been reported as a good prognostic factor in European studies, although sex has not been shown to affect the efficacy of adjuvant chemotherapy in a subset analysis of a phase 3 Japanese study.

The other more commonly held opinion—especially among Japanese researchers—is that disparity in gastric cancer treatment outcomes between east-Asian and western countries are related to the use of population screening in Japan, differences in the approach to surgery and adjuvant therapy, and differences in efficacy and tolerance to anticancer drugs against gastric cancer. Since the introduction of a nationwide screening programme in 1983, a progressive stage migration of gastric cancer towards an early stage at diagnosis has been noted in Japan, where over 40% of cases are localised at diagnosis compared with around 25% in the USA.

Differences in surgical practice between Japan and western countries

Endoscopic mucosal resection, a minimally invasive technique pioneered by Japanese surgeons, has been widely used in Japan for treating up to 50% of stage IA gastric cancers detected at screening. Such an approach has limited applicability in the west because most patients are diagnosed when their disease is at an advanced stage. Gastrectomy with the systematic dissection of lymph nodes, known as D2 dissection, is the standard surgical technique used in Japan, whereas D1 dissection is the standard in most western countries. Randomised and non-randomised studies in the west have been unable to reproduce the excellent 5-year survival of up to 69% reported in Japan with D2 dissection.

Differences in surgical technique and outcomes can affect how adjuvant trials are done and interpreted. Randomised trials from western regions have shown a significant survival benefit of adjuvant chemoradiation or intensive peri-operative combination chemotherapy with the epirubicin, cisplatin, and fluorouracil (ECF) regimen. However, baseline surgical quality and outcomes were quite different from those in Japan, and Japanese oncologists have not accepted the western results. This is because in Japan, most patients present at an early stage that is amendable to primary surgery without the need for downstaging with neoadjuvant chemotherapy, therefore primary surgical resection and post-operative chemotherapy alone is considered the standard. This is in sharp contrast with practice in the UK and Europe, where neoadjuvant strategies are more popular, while in the US, D1 dissection followed by post-operative chemoradiation is favoured.

Differences in tolerance to chemotherapy for gastric cancer

Differences in tolerability to postoperative chemotherapy exist between Japanese and non-Japanese populations. Physiological differences and the lower incidence of postoperative complications might explain why Japanese patients are known to tolerate adjuvant chemotherapy much earlier after surgery than non-Asian patients. Another possible reason is the preference for less toxic adjuvant chemotherapy regimens in Japan, such as the use
of single agent intravenous or oral fluorouracil,53 by contrast with the use of multi-agent chemotherapy in the west. This difference in preference for certain chemotherapeutic agents has also led to disparities in the results of randomised trials of new drugs for advanced gastric cancer. The control group in most non-Japanese studies often consists of cisplatin-based doublets or triplets, whereas single-agent fluorouracil or S-1 alone is used in Japanese trials. The platinum-based triplets DCF (docetaxel, cisplatin, and fluorouracil)54 and ECF55 are now the standard of care in the USA and UK, respectively, based on their survival benefit in randomised studies. However, such regimens are often considered by Japanese oncologists to be too toxic and to confer only modest benefits.

S-1 is an oral fluoropyrimidine composed of tegafur, 5-chloro-2,4-dihydroxypyridine, and potassium oxonate at a molar ratio of 1:0·4:1. This drug was developed and is widely used in Japan, but is not yet approved in the west. Interestingly, phase 1 studies of S-1 in Japan and the USA56–58 have reported regional differences in its dose-limiting toxicity, where myelosuppression was more common among Japanese patients and diarrhoea in western patients, with the overall risk of toxicity higher in Americans and Europeans. This disparity might be due to a difference in pharmacokinetics, as Americans and Europeans have a higher AUC of fluorouracil (the active metabolite of S-1) following treatment with much lower doses of S-1 than Japanese patients. In turn, this might be due to the fact that the conversion rate of tegafur to fluorouracil differs in Asian (Japanese) and white (Dutch) patients because of polymorphic differences in the CYP2A6 gene.59 Another possibility is that American patients tend to have a higher body surface area than Japanese patients.60 Interestingly, the pharmacokinetic data in a US phase 1 study found that potassium oxonate, the agent in S-1 which supposedly reduces diarrhoea, can be metabolised to a potentially toxic metabolite.61

### Implications for clinical practice
Pharmacogenomic studies have shown that there is a high degree of genetic diversity in drug-metabolising genes between different ethnic groups (table 1), thus raising the

<table>
<thead>
<tr>
<th>Drug transporter</th>
<th>Prevalence of allelic types</th>
<th>Phenotype association</th>
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<tbody>
<tr>
<td>CYP2D6</td>
<td>Three allelic types: wt/wt (55%); wt/*17 (36%); and *17/*17 (9%)</td>
<td>Absent null alleles associated with intact formation of active tamoxifen metabolites; harbouring one or more null alleles (*4/*5 linked to impaired formation of active tamoxifen metabolites and poor survival after adjuvant tamoxifen; *10/*10 allele confers increased risk of disease recurrence after adjuvant tamoxifen and impaired formation of active tamoxifen metabolites62 carriers of *12/*17 have increased enzyme activity and better survival after adjuvant tamoxifen compared with carriers of other alleles63 2/*2 triples the risk of death with adjuvant tamoxifen compared with other genotypes64</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Three allelic types: wt/wt (55%); wt/*17 (36%); and *17/*17 (9%)</td>
<td>Carriers of *12/*17 have increased enzyme activity and better survival after adjuvant tamoxifen compared with carriers of other alleles63</td>
</tr>
<tr>
<td>SULT1A1</td>
<td>Three allelic types: *1/*1 (43%); *1/*2 (43%); and *2/*2 (14%)</td>
<td>*1/*2 triples the risk of death with adjuvant tamoxifen compared with other genotypes64</td>
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<tr>
<td>XR*1B</td>
<td>Three allelic types: *1/*1 (43%); *1/*2 (47%); and *2/*2 (20%)</td>
<td>Reduced activity of PXR and its downstream targets CYP3A4 and ABCB1; lower clearance of doxorubicin65</td>
</tr>
<tr>
<td>SLC22A16</td>
<td>c.1466G; c.1226T&gt;C (wt) and c.1466G; c.1226T&gt;C (het)</td>
<td>c.1466G variant: associated with increased AUC of doxorubicin and doxorubicinol concentrations66</td>
</tr>
<tr>
<td>UGT1A1*28</td>
<td>Three allelic types: wt/TA (6/6); heterozygote TA (6/7); homozygote TA (7/7)</td>
<td>Carriers of TA(7/7) are 7–9 times more likely to experience severe diarrhoea41 and neutropaenia44 after irinotecan;40,41 they also have a higher AUC of SN38,41 and lower SN38 glucuronidation rates than non-carriers41</td>
</tr>
<tr>
<td>DPYD*2</td>
<td>Three allelic types: wt/TA (6/6); heterozygote TA (6/7); homozygote TA (7/7)</td>
<td>Prevalence of UGT1A1*28 polymorphisms: North American and Europeans 40–50%, Japanese and Chinese &lt;20%</td>
</tr>
<tr>
<td>TYMS*</td>
<td>Three allelic types: wt/TA (6/6); heterozygote TA (6/7); homozygote TA (7/7)</td>
<td>Prevalence of UGT1A1*28 polymorphisms: North American and Europeans 40–50%, Japanese and Chinese &lt;20%</td>
</tr>
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- **EGFR**=epidermal growth factor receptor. **SULT**=sulfotransferase 1A1. **SLC22A16**=solute carrier family 22. **UGT1A1**=uridine diphosphate glucuronosyltransferase. wt/wild-type. **PXR**=pregnane X receptor. **DPYD**=dihydropyrimidine dehydrogenase. **MDR1 (ABCB1)**=multidrug-resistance gene. **TYMS**=thymidylate synthase gene. **CIR1=carboxyl reductase 1 gene. AUC=area-under-curve concentration.

**Table 1**: Inter-ethnic differences in the prevalence of selected genetic variants that affect response and/or toxicity to anticancer drugs
patients with metastatic colorectal cancer who are to be treated with irinotecan, with the intent of modifying the dose as a way to avoid adverse drug reactions”.\textsuperscript{30} It should also be emphasised that while the main distinction between populations lies in the prevalence of these predictive genotypes, this observed relationship between specific genotypes and response to treatment is expected to be similar across populations.

Most of the pharmacogenomic studies described in this review are retrospective, case–control studies, the sample sizes of which are often inadequately powered for allowing multiple comparisons across many different SNPs and haplotypes. This results in inconclusive and sometimes contradictory results. The Gastrointestinal Scientific Leadership Council of the Coalition of Cancer Cooperative Groups has highlighted the need for more prospective pharmacogenomic studies in colorectal cancer, developing more advanced bioinformatics tools for evaluating genotype–phenotype relationships, and establishing the population-based tissue and blood archives and clinical databases that are necessary for adequately-powered studies on inter-ethnic variations in pharmacogenomic biomarkers.\textsuperscript{30}

### Table 2: Population-based differences in drug tolerance and treatment outcome following anticancer drug therapies, and the associated causes of such differences

<table>
<thead>
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<th>Biological</th>
<th>Environmental/epidemiological</th>
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<tr>
<td>Lung cancer</td>
<td>High prevalence of EGFR tyrosine kinase mutations in Asian female non-smokers</td>
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<tr>
<td>Breast cancer</td>
<td>High incidence of taxane-related neutropenia in Asians</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>Pharmacogenomic variations affecting clinical outcome with hormonal therapy, and toxicity from chemotherapy</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>Higher incidence of severe toxicities from fluoropyrimidines in trial centres outside the USA (eg, east Asia); pharmacogenomic variations affecting toxicity from irinotecan and fluoropyrimidines</td>
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<tr>
<td></td>
<td>Tolerance of post-operative chemotherapy better in Japanese studies than in western studies, possibly due to differences in body-surface area</td>
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EGFR=epidermal growth factor receptor; ECF=epirubicin–cisplatin–fluorouracil; DCF=docetaxel-cisplatin-fluorouracil.

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### Table 3: Practical implications of population-based differences in anticancer drug tolerance and treatment outcome

<table>
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<th>Possible implications</th>
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<tr>
<td>Lung cancer</td>
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<td>Gastric cancer</td>
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Implications in drug development

As documented in the International Conference on Harmonisation—Ethnic Factors in the Acceptability of Foreign Clinical Data, there is a practical need to acknowledge differences between the uses of medicines in different regions of the world. The approval of new oncology drugs depends on the attainment of key efficacy and safety endpoints such as survival, response rate, and toxicity. Therefore, judicious selection of study patients and study treatment (in terms of dosage, schedule, choice of comparator groups) is crucial for the successful translation of new drugs. Population-based differences in biological factors such as target expression can have a significant effect on study outcome and data interpretation. The clinical development of gefitinib in lung cancer is a good example of the importance of how careful patient selection based on their demographic (eg, Asian non-smokers), pathological (eg, adenocarcinoma) and molecular profiles (eg, activating EGFR tyrosine kinase mutations), can make the difference between meeting or not meeting study endpoints. Differences in the incidence of drug toxicity and altered pharmacokinetics between groups of different ethnic origin point to the increasing need for the systematic prospective collection of blood samples for the assessment of pharmacogenomics, and also points to the need for clinical trials from the phase 1–3 level outside western countries. Molecular epidemiological studies using clinical data and creating large tumour-sample repositories from specific populations are also required. These activities rely on support from multinational cooperative groups, academic bodies, the government, and the pharmaceutical industry. However, multinational cooperative studies can be complicated by regional differences in tumour biology, standards of care, and drug-approval requirements. These complications might be resolved by introducing more flexibility in trial design (such as the use of “dealer’s choice” of control group), or by doing parallel registrational studies in western and Asian populations.

Conclusion

This review has highlighted some key population-based differences in the tolerance and clinical outcome to anticancer drugs (table 2). The many factors that contribute to these differences can be regarded as either biological (eg, variations in physiology, pharmacogenomics, and tumour biology) or environmental (eg, socioeconomic factors, regional differences in treatment standards). These differences can have important implications for clinical practice and the development of new drugs in oncology (table 3).

In summary, population-based differences have become an essential consideration in the development of modern anticancer drugs, and are an important factor in clinical decision-making with regards to implementing new therapeutic recommendations. These differences reflect the diversity and complex interplay of biological and socio-cultural characteristics of the human race and human diseases.

Search strategy and selection criteria

Data for this Review were identified by searches of PubMed, and references from relevant articles using the search terms “ethnic differences/disparities”, “population”, “racial differences/disparities”, “pharmacogenomics”, “biology”, “treatment outcome”, and “lung/breast/gastric/colorectal cancer”. Abstracts and reports from meetings were included only if they were recently reported, phase 3 trials or large cohort studies with potentially important, innovative, or previously unpublished results, and only if they were essential for illustrating specific points. Papers published in English between January, 1980, and March, 2009, were included.

References

Review


