Dietary soya isoflavones and breast carcinogenesis: a perspective from a cell-culture model

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Southeast Asian women have a lower incidence of breast cancer than their counterparts in the West. Epidemiological studies have indicated that soya consumption may be a contributing factor. Carcinogenesis is a process involving multiple stages. The present review attempts to fit the cellular mechanisms attributed to soya isoflavones into these different stages. Many cell-culture studies have reported the growth-inhibitory effect of soya isoflavones; however, with the non-physiological concentrations employed in these studies it would be difficult to explain the protection mechanisms observed in epidemiological studies. Our laboratory has previously found that genistein inhibits cytochrome P450 (CYP)1A1 and CYP1B1. The inhibition implies that soya consumption may have the potential to prevent chemical carcinogenesis. The preferential inhibition of CYP1B1 may also block the oestrogen-initiated carcinogenesis. The antagonism of oestrogen receptor (ER) binding can affect the cell-proliferative phase, which is likely to be important in the promotion stage of breast cancer. Since our laboratory and others have indicated that genistein at physiological concentrations has no effect on the downstream activities of ER binding, the antagonism of ER is not likely to be a contributing factor in the disease prevention. Moreover, soya isoflavones cannot inhibit aromatase (CYP19), which is the enzyme responsible for oestrogen synthesis. In the present review various cellular activities altered by soya isoflavones are discussed.

Soya isoflavones: Breast cancer: Cell-culture models

Introduction
Breast cancer is one of the most common cancers in women. Asian countries have lower breast cancer incidences than the West; however, no difference in breast cancer incidence is found between Asian descendants and other women in America (Ziegler et al. 1993). These results suggest that the environment may play a part in the aetiology of breast cancer, and diet has been one of the major leads of investigation.

Epidemiological studies indicate that the consumption of some phytochemicals protects against cancer. A lower incidence of human cancers is associated with increased consumption of vegetables, fruits and beans (Kuo, 1997). The American Cancer Society (1993) has reported a lower incidence of breast cancer in the female population of Southeast Asia than those in Europe and America. One specific dietary area that epidemiologists have extensively investigated is the difference in soya consumption. Among the compounds isolated from soya beans, isoflavones have drawn the most attention for their cancer prevention activity. Animal studies have elicited conflicting results on the cancer-protective effect of soya isoflavones. Although prepubertal administration of genistein could reduce breast cancer incidence in rats treated with 7,12-dimethylbenz[a]anthracene (DMBA) (Hilakivi-Clarke, 2000; Lamartiniere et al. 2002), soya given after weaning appears to be ineffective (Appelt & Reicks, 1999). In contrast, Gallo et al. (2001) have shown that genistein does not protect against DMBA-induced mammary tumour incidence or multiplicity, but it reduces the percentage of poorly differentiated tumours. In a recent study, daidzein and soya protein rather than genistein have been suggested to be the active ingredients in soya beans that reduce the multiplicity of DMBA-induced mammary tumours in rats (Constantinou et al. 2001). Nevertheless, both daidzein and genistein are effective in delaying the latency of mammary tumour

Abbreviations: AHR, aryl hydrocarbon receptor; Cdk, cyclin-dependent kinase; CYP, cytochrome P450; DMBA, 7,12-dimethylbenz[a]anthracene; ER, oestrogen receptor; ERE, oestrogen response element; JNK, c-Jun N-terminal kinase; PAH, polycyclic aromatic hydrocarbons.

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development in a spontaneous carcinogenesis model, although the size and number of tumours are similar at the end of the experiment (Jin & MacDonald, 2002). In contrast, genistein has been shown to increase DMBA-induced mammary tumours in oestrogen receptor (ER) α-intact mice (Day et al. 2001), and encourages the proliferation of MCF-7 and N-nitroso-N-methylurea-induced tumours respectively in athymic mice (Ju et al. 2001) and Sprague–Dawley rats (Allred et al. 2004). These reports appear to be inconsistent regarding the chemopreventive effect of genistein, but the confounding results could be caused by the phytochemical’s differential actions on the initiation, promotion, and progression stages.

As illustrated in Fig. 1, breast carcinogenesis can be divided into multi-stages. During the initiation stage, various agents introduce gene mutation in the cell and no morphological changes can be observed in this stage. In the promotion–progression stage, a clonal expansion of these genetically altered cells occurs to form pre-neoplastic and neoplastic cells before growing into an invasive cell mass. Gene–environment interaction plays an important role in the aetiology of cancer, and diet is an inseparable part of this interaction.

**The effect of soya isoflavones in the initiation phase**

Events that lead to a permanent alteration of DNA are considered to represent the initiation phase of cancer. Long-term exposure to some environmental and dietary compounds has been linked to higher incidence of human breast cancer. Soya isoflavones are protective against cancer initiators in most investigations, while other studies indicate that their metabolites can be mutagenic.

**Polycyclic aromatic hydrocarbon toxicity**

Polycyclic aromatic hydrocarbons (PAH) are commonly found in our environment, and they can be isolated from diesel exhaust, barbequed meat, tobacco smoke, overheated cooking oil, etc (International Agency for Research on Cancer, 1983; Environmental Protection Agency, 1990). PAH are metabolised and transformed into DNA-attacking electrophiles in the body. The significance of these environmental toxicants in breast cancer can be inferred from the increased presence of PAH–DNA adducts in human breast tumours (Li et al. 1996).

Aryl hydrocarbon receptor (AHR) is a mediator in the transformation of procarcinogens to genotoxic moieties. After binding to a PAH, the cytosolic AHR translocates to the nucleus and dimerises with an AHR nuclear translocator. The dimerisation initiates transcription of a gene containing xenobiotic responsive elements in its promoter region (Kronenberg et al. 2000). Cytochrome P450 (CYP) 1A1 and CYP1B1 enzymes, which are responsible for the biotransformation of PAH, are downstream genes of AHR transactivation (Dertinger et al. 2000; Safe, 2001). The importance of AHR and CYP1B1 enzyme in PAH-induced carcinogenesis is implicated in results of studies in two gene-knockout mice; benzo[a]pyrene cannot induce cancer in AHR-null mice (Shimizu et al. 2000), and lower cancer incidence has been observed in DMBA-treated CYP1B1 knockout mice (Buters et al. 1999).

The inhibition of CYP1 enzymes appears to be beneficial in the prevention of DMBA–DNA adduct formation in vivo and in vitro (MacDonald et al. 2001; Kleiner et al. 2002). Polymorphisms with high activity of CYP1A1 have been shown to be a risk factor for breast cancer in African-Americans (Taioli et al. 1999) and Chinese (Huang et al. 1999). CYP1B1 polymorphisms have also been associated
with breast cancer risk in the Nurses’ Health Study cohort in the USA (Huber et al. 2002) and among the Chinese women studied in Shanghai (Zheng et al. 2000).

Our in vitro model has shown that genistein reduces DMBA–DNA adduct formation and the chemopreventive mechanism may be attributed to its interruption of DMBA metabolism as shown in Fig. 2. Daidzein, on the other hand, is non-functional in this regard. Genistein down regulates CYP1A1 and 1B1 mRNA expression at 25 μmol/l through its influence on xenobiotic responsive element-dependent transcriptional control. At the enzyme level, kinetic studies have indicated that the Ki values of CYP1A1 and 1B1 are 15·35 and 0·68 μmol/l, respectively (Chan & Leung, 2003). Genistein appears to preferentially inhibit CYP1B1 to CYP1A1 as denoted by the Ki values, and the low Ki value for CYP1B1 inhibition implicates an achievable plasma concentration through diet. CYP1B1 expression in the mammary gland has been shown to be higher than that in the liver (Horn et al. 2002), and is both inducible and constitutively expressed. This may imply that the isoflavone offers a stronger protection against PAH-induced carcinogenesis in the mammary gland than in the liver.

A structure–inhibitory activity relationship between CYP1 enzymes and isoflavones has been described in xenobiotic-induced hepatic S9 fraction (Lee et al. 1994). The hydroxyl groups at the C4’ and C7 positions of the isoflavone molecules and the phenolic group at C5 are critical for the inhibitory action of 7-ethoxyresorufin O-deethylase (Chae et al. 1992; Lee et al. 1994). As a result, daidzein that has hydroxyl groups at positions 4’ and 7 but lacking a C5 hydroxyl group may not be as active as genistein.

**Oestrogen-induced DNA damage**

Oestrogen can be hydroxylated into 2, 4, and 16α-OH metabolites. These catechol oestrogen metabolites can further be oxidised to the quinone and semiquinone structures that are genotoxic and carcinogenic in animal models (Liehr et al. 1986; Li & Li, 1987). Some metabolites retain oestrogenic activity, and may also generate mutagenic free radicals as well (Zhu & Conney, 1998). As reviewed by Liehr (2000), two major CYP enzymes that are responsible for the hydroxylation of oestrogen are CYP1A1 (oestrogen-2-hydroxylase) and CYP1B1 (oestrogen-4-hydroxylase). The DNA-damaging effect of oestrogen has been demonstrated in MCF-7 cells (Yared et al. 2002) and rat mammary tissues (Zhang et al. 2001). The inhibition of CYP1B1 enzymes by genistein may protect the cells from DNA damage produced by 4-OH oestrogen (Fig. 2).

**DNA damage caused by soya isoflavones**

Consuming high amount of soya isoflavones may also present undesirable effects in the initiation stage of carcinogenesis. The soya isoflavone metabolites orobol and 7,3’,4’-OH isoflavone can bring about oxidative DNA damage at 10 μM in human mammary epithelial MCF-10A cells (Murata et al. 2004). However, the concentration employed is above the physiological concentration.

**Perturbation at the promotion–progression phase**

In the multi-stage carcinogenesis model, mere occurrence of genetic alteration is not sufficient to progress to cancer. Some endogenous or exogenous stimuli must be present to facilitate clonal proliferation of the cells bearing mutated genes. The effect of soya isoflavones in this stage of carcinogenesis has been controversial.

**Oestrogen receptor binding**

Excessive and cumulative exposure to oestrogen has been regarded as a risk factor of breast cancer (Yager, 2000). In vivo and in vitro studies have associated increased incidence of breast cancers with oestrogen (Colditz, 1999). This cause-and-effect phenomenon has again been supported by results from a recent study in a transgenic model (Yoshidome et al. 2000).

ER is an intranuclear binding protein with a DNA-binding domain and a ligand-binding domain (Pike et al. 2000a,b). When a ligand binds onto the specific domain, the ER protein will undergo conformational changes and initiate transcription by attaching to an oestrogen response element (ERE) in the promoter region of oestrogen-sensitive genes. Recently, two subtypes of ER designated as α and β have been identified, and their differences in tissue distribution and ligand affinity have been determined in the treatment of oestrogen-related diseases (Dechering et al. 2000). ER-α plays a crucial role in growth and differentiation of the mammary gland, but it also mediates oestrogen-induced carcinogenesis in the breast. In contrast, the role of ER-β in breast cancer has yet to be defined. Pre-malignant breast tissue expresses more ER-α than normal breast tissue (Allred & Mohsin, 2000). The ER-α gene, however, is mostly lost in more advanced types of breast tumour (Sheng et al. 1996). Many studies have shown that genistein is an agonist of ER, both in animal (Makela et al. 1995) and cell-culture models (Wang et al. 1996; Fioravanti et al. 1998; Miodini et al. 1999). Other studies have claimed that genistein is an antagonist of ER. Kuiper et al. (1997) have expressed rat ER-α and -β and found that genistein competes with 17β-oestradiol for the ligand-binding domain of ER-α and -β.
Our laboratory has expressed ER-α and β in HepG2 cells to examine the specific effect of genistein on ER. This cell line has been shown previously to be ER-negative and is useful in the evaluation of ligand–receptor interaction by expressing a specific ER isoform in the cells (Barkhem et al. 1997). We have demonstrated that genistein potentiates ER-α (Po et al. 2002a,b) and -β (LS Po and LK Leung, unpublished results) transactivation with oestriadiol administration. It appears that the replacement of oestradiol by genistein as the ligand of ER does not inhibit the transactivation. Since similar ER transactivation results have been observed for ER-β, the claim that genistein is anti-oestrogenic cannot be substantiated at the cellular level. These results suggest that genistein is a potentiator rather than an antagonist in the ER-initiated nuclear event. In fact, the findings that genistein is oestrogenic at concentrations from 0·1 to 50 μM in the presence or absence of 0·1 nM oestradiol have also been reported by Kuiper et al. (1998) and Le Bail et al. (1998). These results suggest that the receptor-binding replacement of oestrogen by genistein cannot halt the ERE-transactivating events. In fact, genistein alone may initiate the ER–ERE complex formation (Miodini et al. 1999). The complex has been verified to be active from the transcriptions of its downstream oestrogen responsive genes, including PS2 and cathepsin D (Miodini et al. 1999).

The interaction of oestradiol and ER can be multifaceted. Hall et al. (2001) describe at least four known oestriadiol-initiated signalling pathways. Two of these pathways require the transactivation of ER whereas the others are ERE-independent. The transcriptional binding sites, Ap-1 (Paech et al. 1997), Sp-1 (Batistuzzo de Medeiros et al. 1997), raloxifene response element (Yang et al. 1996a,b) and genes containing the antioxidant response element (Montano & Katzenellenbogen, 1997) are all responsive to oestrogen administration. Although genistein is not an effective antagonist of oestradiol on the classical ER-dependent pathways, the possibility that genistein antagonised the ERE-independent signalling pathways cannot be totally ruled out. On the other hand, genistein may selectively generate an activation function-2 surface of ER-β that recruits co-regulators for the repression and activation of transcription (An et al. 2001). Considering the influences on some non-nuclear events of ER, it is still possible that genistein can counteract the downstream events of oestrogen through modulating processes other than those dictated by ERE.

**Oestrogen synthesis and degradation**

Oestrogen can be inactivated by sulfotransferase and sulfatase. Genistein and equol are mixed inhibitors of hepatic oestrogen sulfotransferase within the physiological concentration range (0·5 and 0·4 μM) (Harris et al. 2004).

**Programmed cell death**

Apoptosis is an important process in cancer development and therapy as reviewed by Lowe & Lin (2000). Compounds inducing apoptosis can affect cancer initiation, progression and metastasis. Bcl-2 was the first protein shown to be anti-apoptotic (Reed, 1994). Subsequently, proteins that share structural homology with Bcl-2 have been described and characterised. Bcl-x is one of the Bcl-2 family proteins and has two forms, the long (L) and the short (S) forms. Bcl-x(L) facilitates cell survival, whereas Bcl-x(S) initiates pro-apoptotic signals (Reed, 1998; Reed et al. 1998; Gross et al. 1999a,b). Proteins such as Bax and Bak are pro-apoptotic in many systems, and specific interaction among these proteins can determine cell survival or death (Reed, 1998; Reed et al. 1998; Gross et al. 1999a,b). The cell-death mechanism has been attributed to the release of cytochrome c from mitochondria and the subsequent caspase activation (Li et al. 1997). The interactions among Bcl-2 family proteins can affect the stability of the mitochondrial membrane, which is important in confining cytochrome c to this organelle (Gross et al. 1999a,b). c-Jun N-terminal kinase (JNK) is activated by different stresses such as redox potential alteration, heat shock, osmotic shock, UV irradiation and cytokines. It is activated by phosphorylation carried out by the upstream mitogen-activated protein kinase. A functional JNK can phosphorylate c-Jun, JunD, ATF-2, ATF, ELK1 and Sap-1, and its activity has been associated with apoptosis (Ip & Davis, 1998).

Exposure to oestrogen promotes the development of breast cancer for its cell-proliferative effect (Nenci et al. 1988). One of the proposed mechanisms is in the redirection of apoptotic pathways. 17β-Oestradiol reduces the pro-apoptotic Bak level in MCF-7 cells (Leung et al. 1998) and enhances cell survival by increasing Bcl-2 expression (Wang & Phang, 1995). The latter is due to the direct effect of ER transactivation, because two functional ERE have been located at the Bcl-2 gene promoter region (Perillo et al. 2000).

Studies have shown that genistein displays a proliferative effect at low concentrations (micromolar) (Wang & Kurzer, 1997; Breinholt & Larsen, 1998; Le Bail et al. 1998; Shao et al. 1998) and a growth-inhibitory effect at higher concentrations in MCF-7 cells (Petersen & Barnes, 1991; So et al. 1997). These observations have been interpreted as the agonistic and antagonistic properties of genistein at low and high concentrations, respectively. However, our laboratory (Leung & Wang, 2000; Po et al. 2002a,b) has demonstrated that apoptosis induced by genistein in MCF-7 cells is not related to the classical ER antagonistic effect. By examining the protein expression, we have found that both Bcl-2 and Bax are induced in the cultures. The induction of Bcl-2 can be a result of the oestrogenic effect of genistein. Although genistein may induce phosphorylation and inactivation of Bcl-2 at 150 μM/L, the protein remains functional at the dosages at or below 50 μM (Constantinou et al. 1998). An increased amount of p33 protein, which may be produced by
the activity of JNK, occurs in MCF-7 cells treated with 25 and 50 µmol genistein/l. Because the Bax gene promoter contains a p53-binding region (Miyashita & Reed, 1995), the induction of Bax can be p53-dependent. Besides, Bak protein expression is up regulated while Bcl-x(L) is down regulated by genistein at concentrations at which death is induced. These differential protein expressions with the exception of Bcl-2 favour programmed cell death (Po et al. 2002a,b). Thus, at present, an ER-dependent mechanism of cell death induced by soya isoflavones is not known. Nevertheless, a JNK-mediated stress pathway (Leung & Wang, 2000) may be responsible for the apoptotic response of MCF-7 cells treated with 25 and 50 µM-genistein as illustrated in Fig. 3. At such concentrations, JNK activation may lead to the accumulation of p53 through the MEKK1–JNK signalling pathway (Fuchs et al. 1998). In ER-negative cell lines, genistein can induce cell death in a p53-independent pathway (Li et al. 1999a,b) and up regulate Bax (Li et al. 1999a,b). These studies suggest that genistein can affect multiple pathways which may facilitate or counteract the cell-death process.

Cell-cycle arrest

The cell cycle is a series of events through which cell replication has to undergo. The eukaryotic cell cycle is divided into G1, S, G2 and M phases, and there are checkpoints occurring at different phases to allow progression to the next phase. The tumour suppressor proteins p53 and pRb, cyclins and cyclin-dependent kinases (Cdk) have detrimental effects on the progression of the cell cycle, as reviewed by Hilakivi-Clarke et al. (2004).

In an ER-negative and HER-2-positive cell line derived from human reduction mammoplasty, 10 µM-genistein administration can increase cell number in the sub G0/G1 and the ratio of G0/G1:S + G2/M phases. Increases in the Cdk inhibitor p16INK4 and the Bax:Bcl-2 expression ratio are also evident (Kadare et al. 2002). Genistein has also been found to induce apoptosis in HER-2-expressing MDA-MB-435 cells by up regulating Bax and p21 expression and down regulating Bcl-2 and HER-2–ERBB-2 expression (Li et al. 1999a). High concentrations of genistein are required to induce apoptosis in other breast cells, such as 45 µM for MCG-10F and MCF-12A cells, and 90 µM for MCF-10CA1a and MDA-MB-231 cells. The differential responsiveness appears to be driven by p21, which may also introduce G2-M cell-cycle arrest (Upadhayay et al. 2001).

Cyclin D1 forms a complex with Cdk4/6, which leads to an increased activity of Cdk4 and the subsequent phosphorylation of Rb protein. Cyclin E–Cdk2 complex further phosphorylates Rb and releases E2F transcription factors. Genes inhibited by Rb and involved in entering the S phase are then induced. p21<sup>activ</sup> is a CIP/KIP family protein that can inhibit the cyclin E–Cdk2 kinase activity and prevent the cell from the S phase entry. Effect of high genistein concentration to decrease cyclins D1 and E and induce p21 would arrest the cell cycle at the G1 phase. At the end of the G2 phase, Cdc25C activates Cdc2 by dephosphorylation and triggers the onset of mitosis. Genistein administered in pharmacological concentrations can lead to cell-cycle arrest by way of inducing p21<sup>activ</sup> in MCF-7 and MDA-MB-231 cells (Shao et al. 1998), inhibition of Cdc2 activity and Cdc25C protein expression in MCF-10F cells (Frey & Singletary, 2003). The inhibitory effect on Cdc2 and Cdc25C would stop the cell cycle at the G2-M phase. Fig. 4 summarises the cell-cycle-arresting events introduced by genistein in high dosage. However, Ju et al. (2002) have demonstrated that dietary genistein increases cyclin D in MCF-7 tumours implanted in ovariectomised rats when tamoxifen is co-administered. Increased expression of cyclin D1 and Cdk2 is also reported in MCF-7 cells treated with physiological doses of genistein (Dees et al. 1997). This may facilitate the dysregulation of cell-cycle control. This sharp contrast illustrates that one has to be cautious about the dosages given in cell-culture studies.

BRCA2 expression

High genistein (5 µg/ml) concentration may induce a 60 % increase in BRCA2 mRNA in MDA-MB-231 and MCF-10A cells, but not in MCF-7 cells. Daidzein (20 µg/ml), on the other hand, does not induce any changes in BRCA2 mRNA

Fig. 3. Apoptosis induced by high-dose genistein. JNK, c-Jun N-terminal kinase.
expression. However, no BRCA2 protein increase is evident in these cell lines (Vissac-Sabatier et al. 2003). BRCA2, which is an important tumour suppressor in breast cancer, is not altered by isoflavone administration.

Other active ingredients
Soyasapogenol A and B are sapogenols found in soya beans. Either 10 μM-soyasapogenol A or B inhibits MDA-MB-231 cell growth, while the same stimulates or displays no effect on MCF-7 cells (Rowlands et al. 2002). Soyasapogenol A appears to be oestrogenic because it induces pS2 mRNA expression and forms ER–ERE DNA complexes. Information on their bioavailability or metabolism is not yet available.

Interactions between soya isoflavones and cancer therapeutic drugs
The anti-oestrogen tamoxifen is usually prescribed as an adjuvant therapy for breast cancer patients. It reduces the proliferation of T47D breast cancer cells by inducing G1 cell-cycle arrest. The administration of low-dose genistein may reverse the cell proliferation and cell-cycle arrest (Jones et al. 2002). Soyasapogenol A appears to be oestrogenic because it induces pS2 mRNA expression and forms ER–ERE DNA complexes. Information on their bioavailability or metabolism is not yet available.

Metastasis
Genistein, daidzein, or glycitein at 10 μM or above may inhibit MDA-MB-231 cell adhesion and migration by suppressing the secretion of urokinase-type plasminogen activator through NF-kB and Ap-1 inactivation (Valachovičova et al. 2004).

Bioavailability of soya isoflavones
The dietary relevance of the genistein dosages in human subjects has been established over many years of research. The major soya isoflavone metabolite in women is in the glucuronide form, and the aglycone genistein only constitutes about 25% of total genistein present in plasma (Zhang et al. 2003). In a high-soya-consuming country such as Japan, the average plasma concentration of total genistein is about 0.5 μmol/l in women (Morton et al. 2002). Supplementation may bring about 1 μmol aglycone genistein/l in the plasma of human subjects (Izumi et al. 2000). However, the additive or synergistic effects of various soyabean phytochemicals has not been fully investigated, and such synergy may be sufficient to initiate some physiological changes as

![Fig. 4. Cell-cycle arrest induced by high-dose genistein.](https://www.cambridge.org/core/coreimage)
compared with those observed at high genistein concentrations.

Because a plasma concentration of genistein above 10 \( \mu \text{M} \) is impossible to achieve from dietary intake, the hypothesised events of apoptosis and anti-oestrogenicity produced by soya isoflavones are unlikely to explain differences in breast cancer incidence between women in Western countries and Asia. Effects on CYP1 enzyme inhibition offer a more plausible explanation.

Summary and conclusion

Cellular events induced by high doses of soya isoflavones might not occur in response to dietary consumption alone. The cell model is an empirical system that has advantages as well as disadvantages over other model systems. It may over-simplify the actual function, but it is valuable in identifying the mechanisms involved. Studies have demonstrated that soya consumption is inversely associated with the risk of breast cancer; however, the mechanism is still controversial. The opposite effect at low and high concentrations of soya isoflavones on cell proliferation cannot provide a convincing explanation for the observations in epidemiological studies. Nevertheless, it is still possible that an additive or synergistic chemopreventive effect may occur among dietary compounds. Possible interactions among soya ingredients and other dietary components should be the focus of future investigations.

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