Aromatase inhibitors in breast cancer

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Abstract

The development of aromatase inhibitors for breast cancer therapy is a result of successful translational research exploring the biochemical effects of different compounds in vivo. Studies assessing plasma oestrogen levels as well as in vivo aromatase inhibition have revealed a consistent difference with respect to biochemical efficacy between the third generation compounds (anastrozole, letrozole and exemestane) and the previous, first and second generation drugs, corresponding to the improved clinical effects of these compounds as outlined in large phase III studies. Thus, endocrine evaluation has been found to be a valid surrogate parameter for clinical efficacy. Moreover, the results from these studies have added important biological information to our understanding of endocrine regulation of breast cancer. Based on the clinical results so far, aromatase inhibitors are believed to play a key role in future adjuvant therapy of postmenopausal breast cancer patients and potentially also for breast cancer prevention. Interesting findings such as the lack of cross-resistance between steroidal and non-steroidal compounds should be further explored, as this may add additional information to our understanding of breast cancer biology.

Introduction

The last decade has been a most successful era in the development of endocrine therapy of breast cancer. Improvements include the introduction of novel compounds like the selective oestrogen receptor downregulators (SERDS) (Howell et al. 2002), and further development of medical ovarian suppression in the metastatic as well as in the adjuvant setting (Klijn et al. 2001, Jakesz et al. 2002, Jonat et al. 2002).

However, the most important improvement has been the successful development of third generation aromatase inhibitors in metastatic disease and, more recently, in the adjuvant setting. The successful development of these compounds was based on careful preclinical development (Furet et al. 1993, Njar & Brodie 1999) but, not least, careful evaluation of their in vivo endocrine effects in translational research studies assessing their ability to suppress plasma oestrogen levels, and direct assessment of their effects on in vivo aromatisation, using sensitive methods developed for such purposes (Dowsett et al. 1987, Jacobs et al. 1991, Lønning & Ekse 1995). Studies utilising these assays confirmed the superior biochemical efficacy of the third generation compounds compared with the first and second generation inhibitors (Lønning 1996, Geisler et al. 1998, 2002).

While several contemporary reviews considering the clinical effects of these compounds have been published (Goss & Strasser 2001, Smith & Dowsett 2003), the aim of this paper was to discuss the endocrine and clinical achievements, together with particular emphasis on the importance of translational research in the development of these compounds.

Endocrine rationale for aromatase inhibition

Following the menopause, oestrogens are synthesised in different non-glandular tissues, including liver, bone marrow, muscle, skin, fat and connective tissue (Schweikert et al. 1976, Smuk & Schwers 1977, Perel & Killinger 1978, Frisch et al. 1980, Matsumine et al. 1984) as well as in benign and malignant breast tissue (Perel et al. 1982, Reed et al. 1989, Miller et al. 1990, Bulun et al. 1993). While it has been recognised for many years that the main contributor of the substrate androstenedione is the adrenal gland, there has been some controversy considering the contribution of androgens from the postmenopausal ovary. Based on more
androstenedione, T, testosterone.

recent evidence (Sluijmer et al. 1995, Couzin et al. 2001), it now seems clear that the contribution of the postmenopausal ovaries to circulating androgens is, at best, minor, probably negligible. The main substrate for aromatisation is androstenedione, which is aromatised into oestrone (Fig. 1). While the aromatase enzyme may also aromatise testosterone directly to oestradiol, the fact that androstenedione levels are about fourfold higher compared with testosterone levels in postmenopausal women, and the higher affinity of the aromatase enzyme for the androstenedione substrate, contribute to making oestrone the major circulating unconjugated oestrogen in postmenopausal women (Lønning et al. 1990). While oestrone sulphate exists in higher concentrations (Geisler et al. 1997), this is an inactive conjugate that may act as a depot and (probably) a source of oestrogens to the tissue. When considering circulating oestradiol, it has been estimated that probably half the amount is converted from circulating oestrone, while the residual is produced by direct aromatisation of testosterone (Lønning et al. 1990).

An interesting subject relates to tissue versus plasma oestrogen levels in postmenopausal women. It has been recognised for decades that tissue oestradiol concentration is 10–20 higher compared with circulating oestradiol levels in postmenopausal women (Edery et al. 1980, vanLandeghem et al. 1985, Vermeulen et al. 1985, Miller et al. 1998, Geisler et al. 2001) in contrast to the findings in premenopausal women. The explanation is probably that circulating oestrogens are all synthesised in the tissue; thus, there is a passive ‘gradient’ from tissue toward plasma (Fig. 1), although a study in rats suggested active uptake from the circulation (Masamura et al. 1997). The fact that tumour oestradiol concentration is often higher than the concentration seen in surrounding non-malignant tissue is consistent with local synthesis but also high concentration of the 17β-hydroxysteroid reductase in the tumours (vanLandeghem et al. 1985, Vermeulen et al. 1985). While the aromatase enzyme expressed in different tissues is the same, a number of different promoters have been identified as playing a different role in different compartments (Chen et al. 2001, Bulan et al. 2003), suggesting potential local regulation by hormones, growth factors and interleukins (Reed et al. 1993, Zhao et al. 1995, 1996, Agarwal et al. 1996, Simpson et al. 1999, Singh et al. 1999). Notably, while tissue concentrations of oestradiol are high, we and others have found the concentration of oestrone sulphate to be somewhat lower in tissue compared with the circulation (Vermeulen et al. 1985, Geisler et al. 2001). While this may refute the hypothesis that plasma oestrone sulphate may be taken up by the tissue (Santner et al. 1986), the possibility exists that it may be rapidly metabolised to unconjugated steroids; interestingly, there is evidence that oestrone sulphate may be actively transported across the cell membrane (Pizzagalli et al. 2003). Studies evaluating the quantitative contribution of local oestrogen production in the tumours versus systemic uptake have revealed a substantial inter-individual variation (James et al. 1989, Miller 1994), suggesting that local production plays an important role in some, but not all, tumours.

Compounds

Aromatase inhibitors may be divided into two major classes, the so-called non-steroidal (previously often termed ‘type 2 inhibitors’) and the steroidal compounds (previously termed ‘type 1 inhibitors’) (Fig. 2). The non-steroidal inhibitors belong to two different chemical classes, the so-called aminoglutethimide-like compounds, including aminoglutethimide itself and rogletimide, and triazole derivatives, including anastrazole, letrozole and vorozole. The steroidal compounds are all derivatives of androstenedione, the main substrate for the aromatase enzyme.

The two classes of compounds differ with respect to their biochemical action on the aromatase enzyme. While

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Figure 1 Pathways of oestrogen synthesis in postmenopausal women. E₂, oestradiol; E₁, oestrone; E₁S, oestrone sulphate; A, androstenedione, T, testosterone.

Figure 2 Chemical structure of different aromatase inhibitors.
the non-steroidal compounds bind to the p450 site of the aromatase complex, the steroidal compounds bind to the substrate-binding pocket (Miller 1989). In addition, the steroidal inhibitors can bind irreversibly to the aromatase enzyme (Miller & Dixon 2000), for which reason they are termed ‘suicide inhibitors’ or, more recently, aromatase inactivators. Whether the observed lack of complete cross-resistance between the compounds is related to their action on the aromatase enzyme or whether it could be due to some additional endocrine effects of the steroidal compounds is discussed later in this paper.

Endocrine studies

The efficacy of the different compounds have been assessed in in vitro studies using placental or ovarian tissue with androstenedione as substrate for the enzyme. When compared with aminogluthethimide, the more recent second and third generation compounds were found to be more potent (Batizl et al. 1996). Notably, the differences recorded in in vitro systems may not be directly translated into what may happen in vivo. For the in vivo efficacy of a compound, it should be emphasised that factors other than its direct inhibitory constant, such as total body pharmacokinetics and local tissue penetration, may be of importance.

The endocrine efficacy of different aromatase inhibitors may be assessed in two different ways. One possibility is to determine plasma oestrogen levels; alternatively, we may assess aromatisation directly by double-tracer injections of $^{3}$H-androstenedione and $^{14}$C-oestrone with determination of the isotope ratio in the oestrogens.

When considering plasma oestrogen measurements, the main limitation relates to the sensitivity of the assays. Based on a formal assessment of current methods and plasma oestrogen levels, we have concluded that it is not possible to measure plasma oestrone and oestradiol suppression below 10–15% of control levels in the majority of postmenopausal patients during treatment with the potent third generation aromatase inhibitors and inactivators, despite utilising the most sensitive radioimmunoassays (Lønning 2001). In contrast, the oestrogen conjugate, oestrone sulphate, exists in higher concentrations; here, it is possible to detect up to 99% suppression (Lønning & Ekse 1995). The clinical relevance of this issue is illustrated in a recent paper comparing oestrogen suppression with anastrozole compared with letrozole in a cross-over study (Geisler et al. 2002). For plasma oestradiol, we found no significant difference in suppression between the two compounds due to the fact that most patients had their plasma oestradiol suppressed down to the sensitivity limit of the assays during treatment with both compounds. On the contrary, we were able to detect a significant difference between the compounds with regard to their ability to suppress plasma oestrone and, in particular, oestrone sulphate. When considering oestrone sulphate, we found mean plasma levels during treatment with letrozole to be one-third of the mean level recorded on treatment with anastrozole.

A particular problem relates to oestrogen measurements in patients during treatment with steroidal compounds, such as exemestane. When considering the fact that the dose of drug administered (25 mg/day) is probably around 25 000 times the amount of total estrogens produced in a postmenopausal woman during therapy with such a compound (Lønning et al. 1990), even minor metabolites causing modest interactions in the radioimmunoassays could influence the results. Such interactions have been confirmed with respect to exemestane (Johannessen et al. 1997), and sample purification involving HPLC is always recommended for oestrogen assessment in patients during treatment with such steroidal compounds.

Assessment of in vivo aromatisation may, in principle, be done with one of two methods. One possibility is to infuse $^{3}$H-labelled androstenedione and $^{14}$C-labelled oestrone to achieve a steady-state concentration and to determine the isotope ratio in the plasma oestrone fraction (Santen et al. 1978). The second method is to administer a bolus injection of $^{3}$H-labelled androstenedione and $^{14}$C-labelled oestrone followed by urine collection for 96 h and determination of the isotope ratio in the oestrogen metabolites. In a collaborative programme between Professor Mitch Dowsett’s group in London and our group in Bergen, we used such a method (Jacobs et al. 1991) to determine in vivo aromatase inhibition during treatment with different first, second and third generation compounds. The results are shown in Table 1. A formal assessment of this method confirmed the possibility of detecting up to 99.1% aromatase inhibition in the majority of patients (Dowsett et al. 1995). The sensitivity of the method is illustrated in the recent study comparing anastrozole with letrozole, revealing a significant difference in the degree of aromatisation between the compounds (Geisler et al. 2002). Consideration of the clinical importance of a more complete aromatase inhibition is discussed later in this paper.

Clinical efficacy of second generation aromatase inhibitors/inactivators in metastatic breast cancer

The second generation non-steroidal inhibitor fadrozole and the steroidal inactivator formestane were compared with megestrol acetate as second-line therapy and tamoxifen as first-line therapy. While all these studies
included a limited number of patients by today’s standards, there was no evidence of improved response rate or time-to-progression for any of these compounds compared with ‘standard’ therapy (Pérez-Carrión et al. 1994, Buzdar et al. 1996, Falkson & Falkson 1996, Thürlimann et al. 1996, 1997).

Clinical efficacy of third generation aromatase inhibitors/inactivators in metastatic breast cancer

The results from clinical studies comparing anastrozole, letrozole and exemestane with megestrol acetate or aminoglutethimide in the second-line or tamoxifen in the first-line setting have been reviewed in detail elsewhere (Lønning 2002), and only the conclusion is given here. While the results in the second-line setting are not univocal, in general there is a trend for the superiority of each compound compared with megestrol acetate and for letrozole compared with aminoglutethimide (Buzdar et al. 1998, 2001, Dombernowsky et al. 1998, Gershano-vich et al. 1998, Kaufmann et al. 2000).

The results in the first-line setting seem more convincing. When considering anastrozole, there was a significant improvement for anastrozole compared with tamoxifen regarding time-to-progression in one study, while the compounds were similar in a second (Bonneterre et al. 2000, Nabholtz et al. 2000). Combining the results from the two studies, a significant superiority for anastrozole was revealed in patients harbouring oestrogen receptor-positive tumours (Bonneterre et al. 2001). Summarising the evidence, it may be concluded that anastrozole is at least as good as tamoxifen, although it may be questioned whether it could be claimed to be significantly superior in statistical terms. When considering letrozole, a large phase III study revealed superiority with respect to time-to-progression as well as response rate for letrozole compared with tamoxifen. Importantly, in that study superiority was confirmed in subgroups based on oestrogen receptor analysis, metastatic location and different parameters (Mouridsen et al. 2001). Thus, for letrozole, a clear superiority compared with tamoxifen has been confirmed.

When considering exemestane, a phase II study revealed significant superiority compared with tamoxifen (Dirix et al. 2001). However, the number of patients was small, and the results of the final phase III study in the near future are awaited.

Adjuvant therapy

The results of the large ATAC study have recently been reported (Baum et al. 2002). This study revealed the superiority of anastrozole compared with tamoxifen regarding relapse-free survival when combining local and distant relapses in the statistical analysis (Table 2). So far, no superiority for survival has been recorded but the follow-up time is short, and further analysis is
awaited. Interestingly, in that study, combined treatment with tamoxifen and anastrozole was found to be inferior compared with anastrozole monotherapy, suggesting an antagonistic effect of tamoxifen in patients on anastrozole treatment. The reason for this will be discussed later.

Of particular interest was the profound reduction of contralateral breast cancer seen in the anastrozole arm (Table 2). If this reduction is confirmed during long-term follow-up and also in other studies evaluating aromatase inhibitors for adjuvant therapy, it may suggest aromatase inhibitors as effective agents for breast cancer prevention in postmenopausal high-risk women (see later section).

Currently, several studies comparing letrozole as well as exemestane with tamoxifen given as monotherapy or sequential administration using different time-intervals are being conducted; the results of these studies are expected in the near future.

### Lack of cross-resistance to aromatase inhibitors and inactivators

An interesting observation in metastatic disease has been a lack of cross-resistance between aromatase inhibitors and inactivators, now confirmed in several studies (Table 3).

In general, these studies involved treatment with an aromatase inactivator following failure on an aromatase inhibitor; one small study reported the use of anastrozole in patients failing on formestane (HarperWynne & Coombes 1999). These studies have reported a lack of complete cross-resistance between the different compounds. While the largest study exploring exemestane in patients failing aminoglutethimide, anastrozole or letrozole revealed a small response rate (7%), the percentage of patients achieving stable disease >6 months was 17%, meaning that 24% of the patients benefited from having this therapy implemented following failure on the non-steroidal inhibitor (Lønning et al. 2000). Notably, that study (Lønning et al. 2000) revealed little difference in response rates between patients who had previously failed on a third generation non-steroidal compound versus those who had failed on aminoglutethimide (20 versus 27%). While the findings in some studies that patients failing aminoglutethimide responded to exemestane (Thürlimann et al. 1997b, Lønning et al. 2000) could be explained by a more potent aromatase inhibition with the second compound, the findings that patients may respond

### Table 2 ATAC trial (Baum et al. 2002): Results summary

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>Hazard ratio</th>
<th>95.2% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS in ITT population</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anastrozole vs tamoxifen</td>
<td>0.83</td>
<td>0.71–0.96</td>
<td>0.013</td>
</tr>
<tr>
<td>&gt;Ana + Tam vs tamoxifen</td>
<td>1.02</td>
<td>0.89–1.18</td>
<td>0.8</td>
</tr>
<tr>
<td>DFS in ER+ population</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anastrozole vs tamoxifen</td>
<td>0.78</td>
<td>0.65–0.93</td>
<td>0.005</td>
</tr>
<tr>
<td>Ana + Tam vs tamoxifen</td>
<td>1.02</td>
<td>0.87–1.21</td>
<td>0.8</td>
</tr>
<tr>
<td>Incidence of new contralateral primary breast tumours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anastrozole vs tamoxifen</td>
<td>0.42</td>
<td>0.22–0.79</td>
<td>0.007</td>
</tr>
<tr>
<td>Ana + Tam vs tamoxifen</td>
<td>0.84</td>
<td>0.51–1.40</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Ana, anastrozole; Tam, tamoxifen; ER+, oestrogen receptor positive; CI, confidence interval; ITT, intention-to-treat; DFS, disease-free interval.

### Table 3 Trials evaluating sequential treatment with aromatase inhibitors/inactivators in metastatic breast cancer

<table>
<thead>
<tr>
<th>Treatment and results</th>
<th>AG</th>
<th>AG</th>
<th>AG</th>
<th>AG</th>
<th>nAI</th>
<th>For</th>
<th>nAI</th>
</tr>
</thead>
<tbody>
<tr>
<td>First drug AG</td>
<td>For</td>
<td>For</td>
<td>For</td>
<td>For</td>
<td>Exe</td>
<td>Exe</td>
<td>Exe</td>
</tr>
<tr>
<td>Second drug</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>112</td>
<td>10</td>
<td>78</td>
<td>136</td>
<td>105</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>RR second drug (%)</td>
<td>20.5</td>
<td>20.0</td>
<td>25.6</td>
<td>8.1</td>
<td>4.8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>RR + S.D. ≥ 6 mo (%)</td>
<td>42.9</td>
<td>50.0</td>
<td>60.3</td>
<td>27.2</td>
<td>20.0</td>
<td>62</td>
<td>55</td>
</tr>
<tr>
<td>Reference</td>
<td>I</td>
<td>II</td>
<td>III</td>
<td>IV</td>
<td>V</td>
<td>VI</td>
<td></td>
</tr>
</tbody>
</table>

AG, aminoglutethimide; Ana, anastrozole; Exe, exemestane; For, formestane; nAI, non-steroidal third generation aromatase inhibitors (anastrozole, letrozole and vorozole); RR, response rate; S.D., ≥ 6 months (mo). References for these studies are (I) Murray & Pitt (1995); (II) Geisler et al. (1996a); (III) Thürlimann et al. (1997b); (IV) Lønning et al. (2000); (V) HarperWynne & Coombes (1999); (VI) Carlini et al. (2001).
Correlation between degree of oestrogen suppression and clinical efficacy of treatment with aromatase inhibitors

An important question is whether there is a correlation between response among individual patients and the degree of oestrogen suppression. From a methodological point of view, there are several problems in addressing this question. One issue is the correlation between plasma and intra-tumour oestrogen levels. The ratio between tissue and plasma oestrogen levels varies among individuals (Geisler et al. 2001). To determine tumour oestrogen levels before and during therapy is time and resource consuming; thus, only a limited number of studies including a small number of patients have been conducted so far (Reed et al. 1991, Miller et al. 1998, Geisler et al. 2001, Miller & Dixon 2001). While it seems that in general the degree of tissue oestrogen suppression is of the same magnitude as the suppression of plasma oestrogen levels (Geisler et al. 2001), there is no direct linear correlation between the degree of tissue and plasma oestrogen suppression among individual patients.

Two studies have addressed potential differences in oestrogen suppression among responders and non-responders to aromatase inhibitors. In the first study conducted two decades ago, Santen et al. (1982) found no difference in the degree of oestrogen suppression between the two groups. In the more recent study conducted by an Italian group (Bajetta et al. 2000), somewhat higher pretreatment oestrogen levels in responders compared with non-responders and somewhat higher percentage suppression were found. However, the fact that mean oestrogen suppression in the different groups varied between 35 and 60% in contrast to 80–90% aromatase inhibition revealed by tracer studies (Jones et al. 1992) raises the possibility of non-specific interaction in the hormone assays. Dowsett et al. (1984) found a slight increase in oestrogen and androgen levels in patients relapsing on treatment with aminoglutethimide; however, this was probably due to a non-specific stress reaction.

Clearly, such studies suffer the problem of method sensitivity with respect to tissue as well as plasma oestrogen levels as mentioned above (Lønning 2001). Due to the fact that individual tumours express aromatase activity to a different degree and the finding that tumours may utilise circulating versus locally produced oestrogens to a different degree, this illustrates potential method limitations about correlating plasma oestrogen levels with clinical outcome. Taking into consideration the manifold of mechanisms potentially responsible for endocrine resistance in receptor-positive breast cancers (Geisler & Lønning 2001), it seems unlikely that studies comparing the degree of oestrogen suppression with clinical outcome may add significantly to our understanding. In practice, the only surrogate parameter that could be used for practical purposes in such large-scale studies may be plasma oestrone sulphate (Lønning 2001).

On the contrary, the finding that neither formestane nor fadrozole improved therapeutic efficacy compared with megestrol acetate or tamoxifen, while the third generation aromatase inhibitors and inactivators revealed superiority compared with conventional therapy, clearly suggest a difference in clinical efficacy between those compounds inhibiting in vivo aromatisation by 80–90% and those causing about 98% inhibition.

In conclusion, it seems that a more complete aromatase inhibition is associated with a better clinical outcome although it is difficult to correlate these parameters in individual patients for the reasons mentioned above.

Future directions

Third generation aromatase inhibitors have revealed their superiority in advanced breast cancer. An interesting question is whether treatment of this condition may be further improved. While the third generation compounds inhibit in vivo oestrogen production by > 98%, experimental data have shown that MCF-7 cells exposed to low concentrations of oestradiol over time may adapt to and achieve mitogenic stimulation by oestradiol at a concentration of about $10^{-4}$ of that required for the mother cell lines (Lippman et al. 1976, Masamura et al. 1995). While this suggests that more potent drugs could be beneficial, clinical evaluation of such compounds would be difficult.
for several reasons. One critical factor would be to evaluate their endocrine effects in vivo; considering the sensitivity of today’s assays for hormone measurement as well as in vivo aromatase assessment, it would not be possible to discriminate the biochemical efficacy of such potent compounds from today’s third generation aromatase inhibitors/inactivators.

Interestingly, the in vitro experiments mentioned above (Lippman et al. 1976, Masamura et al. 1995) revealed that growth stimulation by oestriadiol in culture expressed a ‘bell-shaped’ curve; thus, high concentrations inhibited cell growth. Notably, ‘hypersensitised’ cells also expressed a bell-shaped curve, suggesting that oestradiol, at a concentration that would stimulate growth of wild-type cells, would inhibit growth of the ‘sensitised’ ones. Oestrogens administered in pharmacological doses were used for breast cancer therapy before the introduction of anti-oestrogens and aromatase inhibitors (Binnie 1944, Haddow et al. 1944, Ingle et al. 1981). Postulating that some patients developing acquired resistance to aromatase inhibitors may actually be ‘sensitised’, we administered diethylstilboestrol to 32 patients previously exposed to a median of four endocrine regimens. An objective response was obtained in ten patients, with another two experiencing stable disease for >6 months duration (Lonning et al. 2001). The findings illustrate that some patients becoming resistant to aromatase inhibitors still harbour a hormone-sensitive tumour and may benefit from further endocrine treatment.

The results from the ATAC study in the adjuvant setting are exciting, and the follow-up results from this study as well as studies conducted with other aromatase inhibitors are eagerly awaited. Important issues would be not only whether aromatase inhibitors and inactivators reveal superiority with respect to tamoxifen regarding long-term survival, but also whether there could be any difference between the compounds and also whether any type of administration (such as sequential administration of tamoxifen followed by an aromatase inhibitor) may reveal superiority compared with monotherapy.

The findings that the selective oestrogen receptor modulators or SERMs (tamoxifen and raloxifene) reduced breast cancer incidence suggest potential for endocrine therapy as a prevention strategy, particular for postmenopausal women with a high risk of developing breast cancer. The fact that plasma oestrogen levels (Dorgan et al. 2002) as well as bone and breast density (Boyd et al. 1995, Zhang et al. 1997), which may be considered surrogate markers of long-term oestrogen exposure, relate to subsequent breast cancer risk have substantiated the importance of postmenopausal oestrogen levels to subsequent breast cancer development. The recent meta-analysis (Key et al. 2003) revealing a strong correlation between body mass index and plasma oestrogen levels in postmenopausal women raises the interesting question as to whether prevention should be ‘pharmacological’ or more directed at ‘life-style interventions’. It is likely that such issues may be important questions for the medical community as well as health service systems in the future.

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