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Study of adverse outcomes in women using testosterone therapy

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ABSTRACT

Objectives: There are concerns that exogenous testosterone therapy may be associated with adverse cardiovascular effects, increases in risk of breast or uterus cancer and alterations in insulin sensitivity. Objective of this study was to explore the safety of testosterone therapy in actual clinical practice.
Methods: Data from the General Practice Research Database and the Health Improvement Network was used, including computerised medical records of UK general practitioners. The study population included women aged 18+ years prescribed testosterone, administered through implants (72.2%), tablets (18.4%) or injections (7.9%). Each testosterone user was matched by age and practice to three control patients. Cox proportional hazards models were used to compare the rates of several outcomes.
Results: The study population included 8412 women, 2103 testosterone users and 6309 controls. There were no statistically significant differences between the cohorts in the rates of cerebrovascular disease, ischemic heart disease, breast cancer, deep venous thrombosis/pulmonary embolism, diabetes mellitus or acute hepatitis. The rate of breast cancer was comparable between testosterone users and control patients. The rate of androgenic events was increased in the testosterone cohort (relative rate of 1.55 [95% CI 1.21–1.97]). Differences in outcomes between the cohorts were generally comparable across subgroups based on age and use of hormone therapy.
Conclusions: This study found no major increase in the risk of cardiovascular diseases or breast cancer in women using testosterone (implants, tablets, or injections), while the risk of androgenic events was increased. It would be useful to conduct similar studies at lower doses with transdermal testosterone.

1. Introduction

Several randomised clinical trials have reported that testosterone administration to postmenopausal women improves libido and sexual function [1–4]. The European Agency for the Evaluation of Medical Products recently approved a testosterone patch as a therapy for hypoactive sexual desire. However, there are concerns that exogenous testosterone therapy may be associated with adverse cardiovascular effects, increases in the risk of cancer of the breast and uterus, and alterations in insulin sensitivity [5]. While androgen replacement therapy has been used in clinical practice for several years (administered through implants, tablets or intramuscular injections), there are only limited safety data available from comparative studies. The objective of this study was to explore the safety of testosterone therapy (implant, tablet or injection) in actual clinical practice.

2. Methods

This study used data from two UK general practice research databases: the General Practice Research Database (GPRD) and the Health Improvement Network (THIN) research database. Both databases comprise the computerised medical records of general practitioners (GPs) (but other organisations now collect the data from the general practices). GPs play a key role in the UK health care system where they are responsible for primary health care and specialist referrals. Patients are semi-permanently affiliated to a practice, which centralizes the medical information from the GPs, specialist referrals and hospitalizations. The data recorded in the GPRD and THIN include demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions and their major outcomes [6].

The study population consisted of all women aged 18 years or older with a prescription for testosterone during the period of data collection. Testosterone prescriptions were selected from the British National Formulary category 6.4.2: oral testosterone undecanoate, intramuscular testosterone enantate and propionate, testosterone implants and mesterolone. The index date (start of follow-up) of the testosterone users was the first testosterone pre-

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scription. Each testosterone user was matched by age and practice to three control patients. The start of follow-up of the control patients was that of the index date of the matched testosterone user. The two study cohorts were followed from the index date until the date of the outcome of interest or the end of data collection, whichever came first. Cases were patients with the following incident events during follow-up:

- breast cancer (ICD 9 categories 174),
- uterus/endometrial cancer (179, 182),
- ischemic heart disease (410, 411, 413, 414) and myocardial infarction (410),
- cerebrovascular disease (430–438) and stroke (430–434, 436),
- deep venous thrombosis or pulmonary embolism,
- acute hepatitis (570),
- diabetes mellitus (250) and
- androgenic events (GP records of acne, hirsutism, alopecia, clitorimegaly and hoarse voice).

All these events have been recently discussed in review articles on the safety of androgen therapy [7].

In the testosterone cohort, period of follow-up time was divided into two groups, based on current and past testosterone exposure, with patients moving over time between these groups. Current exposure was the expected duration of testosterone use plus 3 months following each testosterone prescription. The expected duration of a testosterone prescription was taken as 6 months for implants and 1 month for the other application forms. Past exposure was the duration of time from the end of testosterone exposure up to end of data collection. The past-exposure period was further divided into segments of 6 months.

2.1. Statistical methods

The incidence of events in the testosterone cohort was compared to that of the control cohort using Cox proportional hazard models. For analyses of variables that may change over time, time-dependent analyses were used. Forward Cox regression was used to estimate adjusted relative rates (RR). The following risk factors were included in the forward regression analyses:

- original database (THIN or GPRD),
- body mass index, smoking and alcohol use (where available),
- *breast cancer*: history of early or late menopause, dysplasia or benign neoplasm of breast, recent use (i.e., prescription in the 6 months before) of HRT (oestrogens, British National Formulary 6.4.1.1), progestogens (British National Formulary 6.4.1.2), NSAIDs and number of prescriptions in the year before,
- *uterus/endometrial cancer*: history of early or late menopause, recent use of HRT, progestogens, and number of prescriptions in the year before,
- *ischemic heart disease*: history of diabetes mellitus, hypertension, cerebrovascular disease, high cholesterol, systemic inflammation (rheumatoid arthritis or systemic lupus erythematosis), atrial fibrillation, renal failure, oophorectomy, recent use of HRT, progestogens, lipid lowering agents, cardiac glycosides, anticoagulants, aspirin, NSAIDs or oral glucocorticoids,
- *cerebrovascular disease*: history of diabetes mellitus, hypertension, ischemic heart disease, high cholesterol, systemic inflammation (rheumatoid arthritis or systemic lupus erythematosis), atrial fibrillation, recent use of HRT, progestogens, nitrates, cardiac glycosides, anti-coagulants, aspirin, statins or oral glucocorticoids,
- *deep venous thrombosis or pulmonary embolism*: history of epilepsy, cerebrovascular disease, cancer, renal failure, diabetes, ischemic heart disease, recent use of HRT, progestogens, and number of prescriptions in the year before,
- *acute hepatitis*: recent use of HRT, progestogens, NSAIDs and number of prescriptions in the year before,
- *diabetes mellitus*: history of hypertension, recent use of HRT, progestogens, oral glucocorticoids and number of prescriptions in the year before, and
- *androgenic events*: recent use of HRT, progestogens, oral glucocorticoids and number of prescriptions in the year before.

Table 1
Baseline characteristics of testosterone users and controls.

Characteristics	Testosterone users (n = 2103)	Controls (n = 6309)
Age (years)		
18–34	146 (6.9%)	438 (6.9%)
35–44	559 (26.6%)	1677 (26.6%)
45–54	1048 (49.8%)	3144 (49.8%)
55–64	287 (13.6%)	861 (13.6%)
65+	63 (3.0%)	189 (3.0%)
BMI[a]		
<20	115 (7.4%)	365 (8.6%)
20–25	931 (59.8%)	2521 (59.2%)
≥26	510 (32.8%)	1372 (32.2%)
Smoking history—yes	625 (39.2%)	1411 (31.6%)
Drug use in 6 months prior to baseline		
HRT (oestrogens)	1737 (82.6%)	955 (15.1%)
Progestogens	337 (16.0%)	676 (10.7%)
Medication for diabetes mellitus	25 (1.2%)	75 (1.2%)
Medical history prior to baseline		
Hypertension	413 (19.6%)	823 (13.0%)
Oophorectomy[b]	363 (17.3%)	109 (1.7%)
Bilateral	198 (9.4%)	35 (0.6%)
Cancer	73 (3.5%)	198 (3.1%)
Diabetes mellitus	40 (1.9%)	100 (1.6%)

[a] BMI was missing in 547 testosterone users and 2051 controls; smoking history was missing in 508 testosterone users and 1843 controls.
[b] Unilateral, bilateral, or unspecified.

In addition to the overall comparison between the testosterone and control cohorts, the patterns of the risks over time were evaluated. The objective of this analysis was to detect any signals of diverging risks over time in the testosterone and control cohorts. In this analysis, patients were followed for the occurrence of the outcomes from start to end of follow-up. For testosterone users, the start of follow-up was the first testosterone prescription and the end of follow-up was the date of censoring. Life-table analysis was used to estimate the cumulative incidence over time.

3. Results

The study population included 8412 women, of whom 2103 were prescribed testosterone and 6309 not using testosterone (control group). The average age of the testosterone users was similar to that of the control women (47.3 years in both groups). The average duration of follow-up in the testosterone cohort after the first testosterone prescription was 4.4 years (median 3.6 years). Testosterone was administered most frequently through implants (72.2% of prescriptions). Tablets accounted for 18.4% and injections for 7.9% of the prescriptions. Methyltestosterone was not used in this population. Table 1 displays the baseline characteristics. The two cohorts were comparable with respect to body mass index and history of cancer, but testosterone users were more likely to use HRT (oestrogens) or have a history of an oophorectomy or hypertension at baseline. About 83% of women using testosterone were prescribed HRT (oestrogens) compared to 15% of the control women.

Table 2
Incidence of outcomes in testosterone and control cohorts.

	Testosterone no. cases (rate[a])	Controls no. cases (rate[a])	Crude RR (95% CI)	Adjusted RR (95% CI)
Cerebrovascular disease	8 (0.1)	22 (0.1)	1.09 (0.49–2.46)	0.95 (0.42–2.17)
Stroke	7 (0.1)	15 (0.1)	1.40 (0.57–3.44)	1.26 (0.51–3.15)
Ischemic heart disease	45 (0.5)	99 (0.4)	1.39 (0.98–1.97)	1.02 (0.70–1.47)
Myocardial infarction	8 (0.1)	21 (0.1)	1.15 (0.51–2.60)	0.88 (0.39–2.02)
Breast cancer	16 (0.2)	52 (0.2)	0.92 (0.53–1.62)	0.78 (0.44–1.37)
Uterus/endometrium cancer	0 (0)	5 (0.01)	–	–
Deep venous thrombosis/pulmonary embolism	13 (0.1)	35 (0.1)	1.13 (0.60–2.13)	0.82 (0.43–1.59)
Diabetes	20 (0.2)	74 (0.3)	0.82 (0.50–1.34)	0.67 (0.41–1.11)
Acute hepatitis	2 (0.02)	6 (0.02)	1.01 (0.20–4.98)	1.01 (0.20–5.02)
Androgenic events	103 (1.2)	194 (0.7)	1.62 (1.27–2.06)	1.55 (1.21–1.97)
Acne	39 (0.4)	69 (0.3)	1.71 (1.15–2.53)	1.65 (1.10–2.46)
Hoarse voice	31 (0.3)	57 (0.2)	3.39 (1.31–8.78)	3.34 (1.27–8.80)
Alopecia	27 (0.3)	65 (0.2)	1.25 (0.80–1.96)	1.18 (0.75–1.86)
Hirsutism	9 (0.1)	8 (0.03)	1.65 (1.07–2.56)	1.58 (1.01–2.46)
Clitorimegaly	0 (0)	0 (0)	–	–

[a] Number of cases per 100 patients per year.

Table 2 shows the incidence of outcomes in the testosterone and control cohorts. There were no statistically significant differences between the two cohorts in the rates of cerebrovascular disease, ischemic heart disease, breast cancer, deep venous thrombosis/pulmonary embolism, diabetes mellitus or acute hepatitis. The rate of breast cancer was comparable between testosterone users and control patients (adjusted RR 0.78 [95% CI 0.44–1.37]). The rate of androgenic events was increased in the testosterone cohort (RR of 1.55 [95% CI 1.21–1.97]). The differences in outcomes between the two cohorts were generally comparable across subgroups of patients based on age, use of HRT (oestrogens) or progestogens, and history of oophorectomy or hypertension (Table 3).

Table 4 shows the RR of ischemic heart disease, breast cancer, or androgenic events with different durations of testosterone use and with different time-periods following testosterone discontinuation. There were no major differences in breast cancer risk with increasing duration of testosterone use. There were 460 women who used testosterone for 2.5 years or more and 213 for 5 years or more.

Fig. 1 shows the patterns of risk of the various outcomes over time in the testosterone and control cohorts. The risks of androgenic events were generally increased in the testosterone cohort over the whole period of follow-up compared to the control cohort. The risk of ischemic heart disease was comparable between the two cohorts until about 350 weeks (6.7 years), when it increased in the testosterone cohort (adjusted RR of ischemic disease in the testosterone users with follow-up <350 weeks: 0.80 [95% CI 0.52–1.23]; RR with follow-up >350 weeks: 2.16 [95% CI 1.05–4.46]). In order to further explore the increased risk of ischemic heart disease after 350 weeks of follow-up, we analysed the utilization of testosterone (there were 513 women with at least 350 weeks of follow-up after the first testosterone prescription). There were 16 testosterone users who experienced incident ischemic heart disease after 350 weeks of follow-up. Two patients were current testosterone users at the time of the event (and 14 past users). Five out of the 16 cases had a history of hypertension at baseline and three developed hypertension during follow-up.

4. Discussion

This study explored the safety outcomes of women using testosterone therapy in actual clinical practice. There were no major differences in the rate of ischemic heart disease or breast cancer in women using testosterone compared to control patients. There were no differences in outcomes in women using testosterone concomitantly with HRT or those using it without HRT.

Women with polycystic ovarian syndrome and women with hirsutism have been found to have an increased risk of cardiovascular disease [8,9]. There are only limited data that examined the risk of cardiovascular disease following exogenous administration of testosterone [5,7]. A recent study found that treatment with intra-

Table 3
RR of outcomes in testosterone users compared to the control cohort stratified by age, HRT or progestogens use and history of oophorectomy.

	Adjusted RR (95% CI)					
	Cerebrovascular disease	Ischemic heart disease	Breast cancer	Deep venous thrombosis/pulmonary embolism	Diabetes	Androgenic events
Age						
<50 years	1.52 (0.45–4.85)	1.20 (0.68–2.14)	0.83 (0.38–1.82)	0.40 (0.15–1.11)	0.76 (0.38–1.51)	1.70 (1.28–2.27)
≥50 years	0.43 (0.10–1.91)	0.87 (0.53–1.42)	0.78 (0.33–1.81)	1.48 (0.61–3.61)	0.52 (0.24–1.11)	1.25 (0.79–1.98)
HRT use						
No	1.07 (0.24–4.74)	1.49 (0.90–2.46)	0.72 (0.28–1.86)	1.52 (0.65–3.59)	0.55 (0.22–1.38)	1.89 (1.32–2.71)
Yes	0.51 (0.16–1.65)	0.86 (0.46–1.63)	0.77 (0.34–1.72)	0.56 (0.19–1.64)	0.59 (0.29–1.20)	1.14 (0.75–1.73)
Progestogens use						
No	1.00 (0.41–2.43)	0.99 (0.67–1.48)	0.74 (0.40–1.40)	0.84 (0.42–1.68)	0.73 (0.43–1.24)	1.54 (1.19–2.00)
Yes	1.72 (0.17–17.56)	1.13 (0.38–3.38)	1.04 (0.27–4.00)	0.45 (0.05–4.20)	0.37 (0.08–1.79)	1.60 (0.79–3.25)
Oophorectomy						
No	0.74 (0.28–1.98)	1.13 (0.77–1.67)	0.72 (0.38–1.36)	0.94 (0.48–1.86)	0.69 (0.41–1.18)	1.48 (1.14–1.93)
Yes	0.40 (0.03–5.04)	0.24 (0.07–0.77)	1.09 (0.20–6.00)	0.07 (0.004–1.56)	0.33 (0.04–2.73)	1.19 (0.44–3.25)
Hypertension						
No	0.80 (0.25–2.50)	1.05 (0.62–1.79)	0.56 (0.27–1.17)	0.59 (0.25–1.38)	0.48 (0.20–1.14)	1.66 (1.27–2.16)
Yes	0.97 (0.28–3.39)	0.95 (0.56–1.60)	1.36 (0.52–3.55)	1.56 (0.51–4.76)	0.81 (0.43–1.53)	1.20 (0.65–2.20)

Table 4
RR of outcomes in testosterone users compared to the control cohort stratified by current and past testosterone exposure.

	Adjusted RR (95% CI)					
	Current use of testosterone for 0–2.5 years	Current use of testosterone for 2.5–5 years	Current use of testosterone for 5+ years	0–2.5 years past testosterone use	2.5–5 years past testosterone use	5+ years past testosterone use
Ischemic heart disease	0.71 (0.34–1.47)	0.30 (0.04–2.23)	1.45 (0.45–4.70)	0.90 (0.48–1.68)	1.42 (0.68–2.95)	1.73 (0.86–3.49)
Breast cancer	0.63 (0.18–2.14)	0.50 (0.07–3.69)	1.06 (0.14–7.95)	0.75 (0.27–2.12)	0.91 (0.32–2.60)	0.96 (0.28–3.35)
Androgenic events	1.75 (1.23–2.49)	1.52 (0.66–3.51)	0.99 (0.24–4.07)	1.29 (0.87–1.93)	1.69 (0.93–3.07)	1.70 (0.84–3.45)

muscular testosterone and estrogen for over 1 year was associated with an increased risk of severe atherosclerosis in postmenopausal women. There was no change in risk of atherosclerosis in women treated for less than 1 year [10]. No information was provided on the associations with other applications of testosterone. In this study, only 8% of the prescriptions for testosterone concerned intramuscular injections. We found a small increased risk of ischemic heart disease in testosterone users after 7 years of follow-up, but this was apparent in both current testosterone users and in patients who stopped testosterone more than 5 years before. Also, there was no association between this increased risk of ischemic heart disease and amount of prior testosterone use.

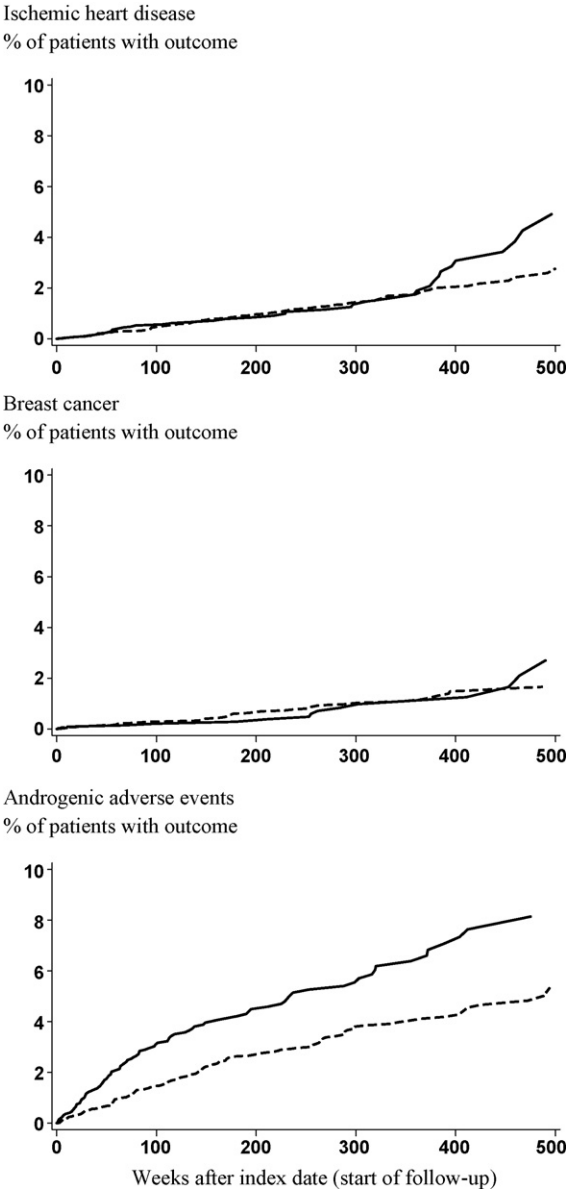

Fig. 1. Patterns of risk of outcome over time in testosterone and control cohorts (*Y*-axis: cumulative incidence over time; *X*-axis: weeks after start of follow-up).

There is a concern that exogenous testosterone may stimulate breast glandular proliferation. On the other hand, animal models have found that testosterone may inhibit growth of breast cancer cells [5,11]. Epidemiological studies that correlated levels of endogenous testosterone with risk of breast cancer have found inconsistent results [5]. For exogenous testosterone, there are only very limited data on the incidence of breast cancer. An uncontrolled observational study of 508 women receiving testosterone found that the incidence of breast cancer over 5 years of follow-up was less than expected based on clinical trial data [12]. In our study, the evaluation of risks over time did not suggest a pattern of increasing rates of breast cancer with use of testosterone. But further data in larger populations are needed.

Androgenic effects are well-known side effects of exogenous testosterone. These effects include acne and hirsutism and are dose-related [7]. In female-to-male transsexuals receiving higher doses, these effects are common. In patients using lower doses, these adverse effects are less common [7]. The results in this study found increases in risk of androgenic events, but that the absolute risk of these evens was low (excess incidence of 0.5%). We found no cases of clitorimegaly.

There are several important limitations of this study. The first limitation is the limited statistical power of this study. It is unlikely that small adverse effects of frequent outcomes and adverse effects of rare outcomes would have been detected in this study. Also, the evidence of this study may not be generalisable to women using testosterone for the treatment of sexual dysfunction, as patient characteristics may differ. Therefore, it would be useful if this comparative epidemiological study would be replicated in a population of women using testosterone for this indication. Another limitation of this study was that patients were not randomised to the testosterone or control group. Women taking hormones may have a different risk factor profile compared to those who do not [13]. Although we adjusted for various characteristics, residual confounding may have been present. There was a large difference between testosterone users and controls in the use of HRT. The analysis of the pattern of the hazard rates was conducted to evaluate any divergence of risks over time, irrespective of any baseline differences.

Strength of this study was that it was conducted in a population representative of actual clinical practice and the good recording of major clinical outcomes. Although a large randomised clinical trial may have been preferable, there are often substantive differences between patients enrolled in clinical trials and patients in actual clinical practice [14]. It may also be difficult to establish long-term safety in clinical trials due to differential loss of follow-up and loss of comparability. Comparative epidemiological studies may provide useful information to the understanding of the safety of drugs in actual clinical practice [15].

In conclusion, this study found that there was no major increase in the risk of ischemic heart disease or breast cancer in women using testosterone (administered through implants, tables or injections). The risk of androgenic events was increased in women using

testosterone. While these results are reassuring, it would be useful to conduct similar comparative epidemiological studies with transdermal testosterone. This study has not raised any major safety concerns about testosterone use. However, especially for use that lasted many years, the numbers of cases were small, confidence limits were relatively wide, control of confounding was only limited, and increased risks have not been excluded.

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References

[1] El-Hage G, Eden JA, Manga RZ. A double-blind, randomized, placebo-controlled trial of the effect of testosterone cream on the sexual motivation of menopausal hysterectomized women with hypoactive sexual desire disorder. Climacteric 2007;10:335–43.
[2] Kingsberg S, Shifren J, Wekselman K, Rodenberg C, Koochaki P, Derogatis L. Evaluation of the clinical relevance of benefits associated with transdermal testosterone treatment in postmenopausal women with hypoactive sexual desire disorder. J Sex Med 2007;4:1001–8.
[3] Shifren JL, Davis SR, Moreau M, et al. Testosterone patch for the treatment of hypoactive sexual desire disorder in naturally menopausal women: results from the INTIMATE NM1 Study. Menopause 2006;13:770–9.
[4] Davis SR, van der Mooren MJ, van Lunsen RH, et al. Efficacy and safety of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. Menopause 2006;13:387–96.
[5] Braunstein GD. Management of female sexual dysfunction in postmenopausal women by testosterone administration: safety issues and controversies. J Sex Med 2007;4:859–66.
[6] Wood L, Martinez C. The General Practice Research Database. Drug Saf 2004;27:871–81.
[7] Basaria S, Dobs AS. Safety and adverse effects of androgens: how to counsel patients. Mayo Clin Proc 2004;79(Suppl.):S25–32.
[8] Wild RA, Grubb B, Hartz A, Van Nort JJ, Bachman W, Bartholomew M. Clinical signs of androgen excess as risk factors for coronary artery disease. Fertil Steril 1990;54:255–9.
[9] Talbott E, Guzick D, Clerici A, et al. Coronary heart disease risk factors in women with polycystic ovary syndrome. Arterioscler Thromb Vasc Biol 1995;15:821–6.
[10] Hak AE, Westendorp IC, Pols HA, Hofman A, Witteman JC. High-dose testosterone is associated with atherosclerosis in postmenopausal women. Maturitas 2007;56:153–60.
[11] Somboonporn W, Davis SR. Postmenopausal testosterone therapy and breast cancer risk. Maturitas 2004;49:267–75.
[12] Dimitrakakis C, Jones RA, Liu A, Bondy CA. Breast cancer incidence in postmenopausal women using testosterone in addition to usual hormone therapy. Menopause 2004;11:531–5.
[13] Matthews KA, Kuller LH, Wing RR, Meilahn EN, Plantinga P. Prior to use of estrogen replacement therapy, are users healthier than nonusers? Am J Epidemiol 1996;143:971–8.
[14] Bailey KR. Generalizing the results of randomized clinical trials. Control Clin Trials 1994;15:15–23.
[15] Waller PC, Evans SJ. A model for the future conduct of pharmacovigilance. Pharmacoepidemiol Drug Saf 2003;12:17–29.