

## 6. References

- Abramov, Y., Borik, S., Yahalom, C., Fatum, M., Avgil, G., Brzezinski, A. & Banin, E. (2004) The effect of hormone therapy on the risk for age-related maculopathy in postmenopausal women. *Menopause*, **11**, 62–68
- Adams, M.R., Register, T.C., Golden, D.L., Wagner, J.D. & Williams, J.K. (1997) Medroxyprogesterone acetate antagonizes inhibitory effects of conjugated equine estrogens on coronary artery atherosclerosis. *Arterioscler. Thromb. vasc. Biol.*, **17**, 217–221
- Adjei, A.A. & Weinshilboum, R.M. (2002) Catecholestrogen sulfation: Possible role in carcinogenesis. *Biochem. biophys. Res. Commun.*, **292**, 402–408
- Adjei, A.A., Thomae, B.A., Prondzinski, J.L., Eckloff, B.W., Wieben, E.D. & Weinshilboum, R.M. (2003) Human estrogen sulfotransferase (SULT1E1) pharmacogenomics: Gene resequencing and functional genomics. *Br. J. Pharmacol.*, **139**, 1373–1382
- Ahmad, M.E., Shadab, G.G.H.A., Hoda, A. & Afzal, M. (2000) Genotoxic effects of estradiol-17 $\beta$  on human lymphocyte chromosomes. *Mutat. Res.*, **466**, 109–115

- Ahmad, M.E., Shadab, G.G.H.A., Azfer, M.A. & Afzal, M. (2001) Evaluation of genotoxic potential of synthetic progestins-norethindrone and norgestrel in human lymphocytes in vitro. *Mutat. Res.*, **494**, 13–20
- Aitken, J.M., Hart, D.M. & Lindsay, R. (1973) Oestrogen replacement therapy for prevention of osteoporosis after oophorectomy. *Br. med. J.*, **3**, 515–518
- Al-Azzawi, F., Wahab, M., Thompson, J., Whitehead, M. & Thompson, W. (1999) Acceptability and patterns of uterine bleeding in sequential trimegestone-based hormone replacement therapy: A dose-ranging study. *Hum. Reprod.*, **14**, 636–641
- Albert, C., Vallée, M., Beaudry, G., Belanger, A. & Hum, D.W. (1999) The monkey and human uridine diphosphate-glucuronosyltransferase UGT1A9, expressed in steroid target tissues, are estrogen-conjugating enzymes. *Endocrinology*, **140**, 3292–3302
- Alpert, L.C., Schechter, R.L., Berry, D.A., Melnychuk, D., Peters, W.P., Caruso, J.A., Townsend, A.J. & Batist, G. (1997) Relation of glutathione S-transferase alpha and mu isoforms to response to therapy in human breast cancer. *Clin. Cancer Res.*, **3**, 661–667
- American College of Physicians (1992) Guidelines for counseling postmenopausal women about preventive hormone therapy. *Ann. intern. Med.*, **117**, 1038–1041
- Anderson, D., Dobrzynska, M.M. & Basaran, N. (1997) Effect of various genotoxins and reproductive toxins in human lymphocytes and sperm in the Comet assay. *Teratog. Carcinog. Mutag.*, **17**, 29–43
- Anderson, G.L., Judd, H.L., Kaunitz, A.M., Barad, D.H., Beresford, S.A.A., Pettinger, M., Liu, J., McNeeley, G. & Lopez, A.M. for the Women's Health Initiative Investigators (2003) Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures. *J. Am. med. Assoc.*, **290**, 1739–1748
- Anderson, G.L., Limacher, M., Assaf, A.R., Bassford, T., Beresford, S.A.A., Black, H., Bonds, D., Brunner, R., Brzyski, R., Caan, B., Chlebowski, R., Curb, D., Gass, M., Hays, J., Heiss, G., Hendrix, S., Howard, B.V., Hsia, J., Hubbell, A., Jackson, R., Johnson, K.C., Judd, H., Kotchen, J.M., Kuller, L., LaCroix, A.Z., Lane, D., Langer, R.D., Lasser, N., Lewis, C.E., Manson, J., Margolis, K., Ockene, J., O'Sullivan, M.J., Phillips, L., Prentice, R.L., Ritenbaugh, C., Robbins, J., Rossouw, J.E., Sarto, G., Stefanick, M.L., Van Horn, L., Wactawski-Wende, J., Wallace, R. & Wassertheil-Smoller, S. for the Women's Health Initiative Steering Committee (2004) Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The Women's Health Initiative randomized controlled trial. *J. Am. med. Assoc.*, **291**, 1701–1712
- Ariga, N., Moriya, T., Suzuki, T., Kimura, M., Ohuchi, N., Satomi, S. & Sasano, H. (2000) 17 $\beta$ -Hydroxysteroid dehydrogenase type 1 and type 2 in ductal carcinoma in situ and intraductal proliferative lesions of the human breast. *Anticancer Res.*, **20**, 1101–1108
- Arrenbrecht, S. & Boermans, A.J.M. (2002) Effects of transdermal estradiol delivered by a matrix patch on bone density in hysterectomized, postmenopausal women: A 2-year placebo-controlled trial. *Osteoporos. int.*, **13**, 176–183
- Ashby, J., Fletcher, K., Williams, C., Odum, J. & Tinwell, H. (1997) Lack of activity of estradiol in rodent bone marrow micronucleus assays. *Mutat. Res.*, **395**, 83–88
- Asthana, S., Baker, L.D., Craft, S., Stanczyk, F.Z., Veith, R.C., Raskind, M.A. & Plymate, S.R. (2001) High-dose estradiol improves cognition for women with AD. Results of a randomized study. *Neurology*, **57**, 605–612

- van Baal, W.M., Kenemans, P., van der Mooren, M.J., Kessel, H., Emeis, J.J. & Stehouwer, C.D.A. (1999) Increased C-reactive protein levels during short-term hormone replacement therapy in healthy postmenopausal women. *Thromb. Haemost.*, **81**, 925–928
- Badawi, A.F., Cavalieri, E.L. & Rogan, E.G. (2001) Role of human cytochrome P450 1A1, 1A2, 1B1, and 3A4 in the 2-, 4-, and 16 $\alpha$ -hydroxylation of 17 $\beta$ -estradiol. *Metabolism*, **50**, 1001–1003
- Bailey, L.R., Roodi, N., Dupont, W.D. & Parl, F.F. (1998) Association of cytochrome P450 *1B1* (*CYP1B1*) polymorphism with steroid receptor status in breast cancer. *Cancer Res.*, **58**, 5038–5041
- Bakken, K., Alsaker, E., Eggen, A.E. & Lund, E. (2004) Hormone replacement therapy and incidence of hormone-dependent cancers in the Norwegian Women and Cancer Study. *Int. J. Cancer*, **112**, 130–134
- Baldereschi, M., Di Carlo, A., Lepore, V., Bracco, L., Maggi, S., Grigoletto, F., Scarlato, G. & Amaducci, L. for the ILSA Working Group (1998) Estrogen-replacement therapy and Alzheimer's disease in the Italian Longitudinal Study on Aging. *Neurology*, **50**, 996–1002
- Banks, E., Beral, V., Cameron, R., Hogg, A., Langley, N., Barnes, I., Bull, D., Elliman, J. & Harris, C.L. (2001) Agreement between general practice prescription data and self-reported use of hormone replacement therapy and treatment for various illnesses. *J. Epidemiol. Biostat.*, **6**, 357–363
- Banks, E., Barnes, I., Baker, K. & Key, T.J. for the EPIC Working Group on Reproductive and Hormonal Factors (2002) Use of hormonal therapy for menopause in nine European countries. In: Riboli, E & Lambert, R., eds, *Nutrition and Lifestyle: Opportunities for Cancer Prevention* (IARC Scientific Publications No. 156), Lyon, pp. 301–303
- Banks, E., Reeves, G., Beral, V., Bull, D., Crossley, B., Simmonds, M., Hilton, E., Bailey, S., Barrett, N., Briers, P., English, R., Jackson, A., Kutt, E., Lavelle, J., Rockall, L., Wallis, M.G., Wilson, M. & Patnick, J. (2004) Influence of personal characteristics of individual women on sensitivity and specificity of mammography in the Million Women Study: Cohort study. *Br. med. J.*, **329**, 477
- Barnabei, V.M., Grady, D., Stovall, D.W., Cauley, J.A., Lin, F., Stuenkel, C.A., Stefanick, M.L. & Pickar, J.H. (2002) Menopausal symptoms in older women and the effects of treatment with hormone therapy. *Obstet. Gynecol.*, **100**, 1209–1218
- Barnabei, V.M., Cochrane, B.B., Aragaki, A.K., Nygaard, I., Williams, R.S., McGovern, P.G., Young, R.L., Wells, E.C., O'Sullivan, M.J., Chen, B., Schenken, R. & Johnson, S.R. for the Women's Health Initiative Investigators (2005) Menopausal symptoms and treatment-related effects of estrogen and progestin in the Women's Health Initiative. *Obstet. Gynecol.*, **105**, 1063–1073
- Barrett-Connor, E. (1991) Postmenopausal estrogen and prevention bias. *Ann. intern. Med.*, **115**, 455–456
- Barrett-Connor, E., Wingard, D.L. & Criqui, M.H. (1989) Postmenopausal estrogen use and heart disease risk factors in the 1980s. Rancho Bernardo, Calif, revisited. *J. Am. med. Assoc.*, **261**, 2095–2100
- Benet-Rodriguez, M., Carvajal García-Pando, A., Garcia del Pozo, J., Alvarez Requejo, A. & Vega Alonso, T. (2002) [Hormonal replacement therapy in Spain]. *Med. clin.*, **119**, 4–8 (in Spanish)
- Beral, V., Banks, E., Reeves, G. & Appleby, P. (1999) Use of HRT and the subsequent risk of cancer. *J. Epidemiol. Biostat.*, **4**, 191–210
- Beral, V. and the Million Women Study Collaborators (2003) Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet*, **362**, 419–427

- Beral, V., Bull, D., Reeves, G. & Million Women Study Collaborators (2005) Endometrial cancer and hormone-replacement therapy in the Million Women Study. *Lancet*, **365**, 1543–1551
- Beresford, S.A., Weiss, N.S., Voigt, L.F. & McKnight, B. (1997) Risk of endometrial cancer in relation to use of oestrogen combined with cyclic progestagen therapy in postmenopausal women. *Lancet*, **349**, 458–461
- Bernstein, L.M., Tsyrlina, E.V., Kolesnik, O.S., Gamajunova, V.B. & Adlercreutz, H. (2000) Catecholestrogens excretion in smoking and non-smoking postmenopausal women receiving estrogen replacement therapy. *Steroid Biochem. mol. Biol.*, **72**, 143–147
- Bhasker, C.R., McKinnon, W., Stone, A., Lo, A.C., Kubota, T., Ishizaki, T. & Miners, J.O. (2000) Genetic polymorphism of UDP-glucuronosyltransferase 2B7 (UGT2B7) at amino acid 268: Ethnic diversity of alleles and potential clinical significance. *Pharmacogenetics*, **10**, 679–685
- Biglia, N., Ambroggio, S., Ponzone, R., Sgro, L., Ujcic, E., Dato, F.A. & Sismondi, P. (2003) Modification of serum IGF-I, IGF-BPs and SHBG levels by different HRT regimens. *Maturitas*, **45**, 283–291
- Bilgrami, I., Blower, K., Feng, J., Stefanko, G. & Tan, E. (2004) Changes in the use of hormone replacement therapy in New Zealand following the publication of the Women's Health Initiative Trial. *N.Z. med. J.*, **117**, U1175
- Bläuer, M., Heinonen, P.K., Martikainen, P.M., Tomas, E. & Ylikomi, T. (2005) A novel organotypic culture model for normal human endometrium: Regulation of epithelial cell proliferation by estradiol and medroxyprogesterone acetate. *Hum. Reprod.*, **20**, 864–871
- Bloemenkamp, K.W.M., Rosendaal, F.R., Helmerhorst, F.M., Koster, T., Bertina, R.M. & Vandenbroucke, J.P. (1998) Hemostatic effects of oral contraceptives in women who developed deep-vein thrombosis while using oral contraceptives. *Thromb. Haemost.*, **80**, 382–387
- Bloemenkamp, K.W.M., de Maat, M.P.M., Dersjant-Roorda, M.C., Helmerhorst, F.M. & Kluit, C. (2002) Genetic polymorphisms modify the response of factor VII to oral contraceptive use: An example of gene-environment interaction. *Vasc. Pharmacol.*, **39**, 131–136
- Boland, L.L., Folsom, A.R., Rosamond, W.D. & Atherosclerosis Risk in Communities (ARIC) Study Investigators (2002) Hyperinsulinemia, dyslipidemia, and obesity as risk factors for hospitalized gallbladder disease. A prospective study. *Ann. Epidemiol.*, **12**, 131–140
- Bolton, J.L., Trush, M.A., Penning, T.M., Dryhurst, G. & Monks, T.J. (2000) Role of quinones in toxicology. *Chem. Res. Toxicol.*, **13**, 135–160
- Bosetti, C., Negri, E., Franceschi, S., Trichopoulos, D., Beral, V. & La Vecchia, C. (2001) Relationship between postmenopausal hormone replacement therapy and ovarian cancer. *J. Am. med. Assoc.*, **285**, 3089
- Boyd, N.F., Lockwood, G.A., Martin, L.J., Knight, J.A., Jong, R.A., Fishell, E., Byng, J.W., Yaffe, M.J. & Tritchler, D.L. (1999) Mammographic densities and risk of breast cancer among subjects with a family history of this disease. *J. natl Cancer Inst.*, **91**, 1404–1408
- Bradlow, H.L., Telang, N.T., Sepkovic, D.W. & Osborne, M.P. (1996) 2-Hydroxyestrone: The 'good' estrogen. *J. Endocrinol.*, **150** (Suppl.), S259–S265
- Brinton, L.A. & Hoover, R.N. for the Endometrial Cancer Collaborative Group (1993) Estrogen replacement therapy and endometrial cancer risk: Unresolved issues. *Obstet. Gynecol.*, **81**, 265–271
- Bromley, S.E., de Vries, C.S. & Farmer, R.D.T. (2004) Utilisation of hormone replacement therapy in the United Kingdom. A descriptive study using the general practice research database. *Br. J. Obstet. Gynaecol.*, **111**, 369–376

- Brueggemeier, R.W., Bhat, A.S., Lovely, C.J., Coughenour, H.D., Joomprabutra, S., Weitzel, D.H., Vandre, D.D., Yusuf, F. & Burak, W.E., Jr (2001) 2-Methoxymethylestradiol: A new 2-methoxy estrogen analog that exhibits antiproliferative activity and alters tubulin dynamics. *J. steroid Biochem. mol. Biol.*, **78**, 145–156
- Buist, D.S.M., LaCroix, A.Z., Newton, K.M. & Keenan, N.L. (1999) Are long-term hormone replacement therapy users different from short-term and never users? *Am. J. Epidemiol.*, **149**, 275–281
- Buist, D.S.M., Newton, K.M., Miglioretti, D.L., Beverly, K., Connelly, M.T., Andrade, S., Hartsfield, C.L., Wei, F., Chan, K.A. & Kessler, L. (2004) Hormone therapy prescribing patterns in the United States. *Obstet. Gynecol.*, **104**, 1042–1050
- Burns, G.R.J. (1983) Purification and partial characterization of arylsulphatase C from human placental microsomes. *Biochim. biophys. Acta*, **759**, 199–204
- Bush, T.L. & Barrett-Connor, E. (1985) Noncontraceptive estrogen use and cardiovascular disease. *Epidemiol. Rev.*, **7**, 89–104
- Bush, T.L., Barrett-Connor, E., Cowan, L.D., Criqui, M.H., Wallace, R.B., Suchindran, C.M., Tyroler, H.A. & Rifkind, B.M. (1987) Cardiovascular mortality and noncontraceptive use of estrogen in women: Results from the Lipid Research Clinics Program Follow-up Study. *Circulation*, **75**, 1102–1109
- Byng, J.W., Yaffe, M.J., Lockwood, G.A., Little, L.E., Trichler, D.L. & Boyd, N.F. (1997) Automated analysis of mammographic densities and breast carcinoma risk. *Cancer*, **80**, 66–74
- Byrjalsen, I., Bjarnason, N.H. & Christiansen, C. (1999) Progestational effects of combinations of gestodene on the postmenopausal endometrium during hormone replacement therapy. *Am. J. Obstet. Gynecol.*, **180**, 539–549
- Cameron, S.T., Critchley, H.O.D., Glasier, A.F., Williams, A.R. & Baird, D.T. (1997) Continuous transdermal oestrogen and interrupted progestogen as a novel bleed-free regimen of hormone replacement therapy for postmenopausal women. *Br. J. Obstet. Gynaecol.*, **104**, 1184–1190
- Campagnoli, C., Colombo, P., De Aloysio, D., Gambacciani, M., Grazioli, I., Nappi, C., Serra, G.B. & Genazzani, A.R. (2002) Positive effects on cardiovascular and breast metabolic markers of oral estradiol and dydrogesterone in comparison with transdermal estradiol and norethisterone acetate. *Maturitas*, **41**, 299–311
- Campagnoli, C., Abba, C., Ambroggio, S. & Peris, C. (2003) Differential effects of progestins on the circulating IGF-I system. *Maturitas.*, **46** (Suppl. 1), S39–S44
- Campbell, S. & Whitehead, M. (1977) Oestrogen therapy and the menopausal syndrome. *Clin. Obstet. Gynaecol.*, **4**, 31–47
- Cano, A., Tarin, J.J. & Duenas, J.L. (1999) Two-year prospective, randomized trial comparing an innovative twice-a-week progestin regimen with a continuous combined regimen as postmenopausal hormone therapy. *Fertil. Steril.*, **71**, 129–136
- Cao, K., Stack, D.E., Ramanathan, R., Gross, M.L., Rogan, E.G. & Cavalieri, E.L. (1998) Synthesis and structure elucidation of estrogen quinones conjugated with cysteine, *N*-acetylcysteine, and glutathione. *Chem. Res. Toxicol.*, **11**, 909–916
- Carlini, E.J., Raftogianis, R.B., Wood, T.C., Jin, F., Zheng, W., Rebbeck, T.R. & Weinshilboum, R.M. (2001) Sulfation pharmacogenetics: *SULT1A1* and *SULT1A2* allele frequencies in Caucasian, Chinese and African-American subjects. *Pharmacogenetics*, **11**, 57–68

- Carney, P.A., Tosteson, A.N.A., Titus-Ernstoff, L., Weiss, J.E., Goodrich, M.E., Manganiello, P. & Kasales, C.J. (2006) Hormone therapies in women aged 40 and older: Prevalence and correlates of use. *Maturitas*, **53**, 65–76
- Castagnetta, L.A.M., Granata, O.M., Traina, A., Ravazzolo, B., Amoroso, M., Miele, M., Bellavia, V., Agostara, B. & Carruba, G. (2002) Tissue content of hydroxyestrogens in relation to survival of breast cancer patients. *Clin. Cancer Res.*, **8**, 3146–3155
- Cauley, J.A., Robbins, J., Chen, Z., Cummings, S.R., Jackson, R.D., LaCroix, A.Z., LeBoff, M., Lewis, C.E., McGowan, J., Neuner, J., Pettinger, M., Stefanick, M.L., Wactawski-Wende, J. & Watts, N.B. for the Women's Health Initiative Investigators (2003) Effects of estrogen plus progestin on risk of fracture and bone mineral density: The Women's Health Initiative Randomized Trial. *J. Am. med. Assoc.*, **290**, 1729–1738
- Caulin-Glaser, T., Garcia-Cardena, G., Sarrel, P., Sessa, W.C. & Bender, J.R. (1997)  $17\beta$ -Estradiol regulation of human endothelial cell basal nitric oxide release, independent of cytosolic  $Ca^{2+}$  mobilization. *Circ. Res.*, **81**, 885–892
- Cavalieri, E., Frenkel, K., Liehr, J.G., Rogan, E. & Roy, D. (2000) Estrogens as endogenous genotoxic agents — DNA adducts and mutations. *J. natl Cancer Inst. Monogr.*, **27**, 75–93
- Chakravarti, D., Mailander, P.C., Li, K.M., Higginbotham, S., Zhang, H.L., Gross, M.L., Meza, J.L., Cavalieri, E.L. & Rogan, E.G. (2001) Evidence that a burst of DNA depurination in SENCAR mouse skin induces error-prone repair and forms mutations in the H-ras gene. *Oncogene*, **20**, 7945–7953
- Chang, T.-C., Chen, M., Lien, Y.-R., Chen, R.-J. & Chow, S.-N. (2003) Comparison of the difference in histopathology and cell cycle kinetics among the postmenopausal endometrium treated with different progestins in sequential-combined hormone replacement therapy. *Menopause*, **10**, 172–178
- Chapman, O., Purohit, A., Wang, D.Y., Ghilchik, M.W. & Reed, M.J. (1995) Oestrone sulphatase activity in normal and malignant breast tissues: Relationship with tumour location. *Anticancer Res.*, **15**, 1467–1472
- Chatterton, R.T., Jr, Geiger, A.S., Mateo, E.T., Helenowski, I.B. & Gann, P.H. (2005) Comparison of hormone levels in nipple aspirate fluid of pre- and postmenopausal women: Effect of oral contraceptives and hormone replacement. *J. clin. Endocrinol. Metab.*, **90**, 1686–1691
- Chen, Z.-H., Na, H.-K., Hurh, Y.-J. & Surh, Y.-J. (2005) 4-Hydroxyestradiol induces oxidative stress and apoptosis in human mammary epithelial cells: Possible protection by NF- $\kappa$ B and ERK/MAPK. *Toxicol. appl. Pharmacol.*, **208**, 46–56
- Cheng, Z., Rios, G.R., King, C.D., Coffman, B.L., Green, M.D., Mojarrabi, B., Mackenzie, P.I. & Tephly, T.R. (1998) Glucuronidation of catechol estrogens by expressed human UDP-glucuronosyltransferases (UGTs) 1A1, 1A3, and 2B7. *Toxicol. Sci.*, **45**, 52–57
- Chester, H., Jiang, C., Borland, J.A., Yacoub, M.H. & Collins, P. (1995) Oestrogen relaxes human epicardial coronary arteries through non-endothelium-dependent mechanisms. *Coron. Artery Dis.*, **6**, 417–422
- Chetrite, G.S., Kloosterboer, H.J., Philippe, J.C. & Pasqualini, J.R. (1999a) Effects of Org OD14 (Livial®) and its metabolites on  $17\beta$ -hydroxysteroid dehydrogenase activity in hormone-dependent MCF-7 and T-47D breast cancer cells. *Anticancer Res.*, **19**, 261–267
- Chetrite, G.S., Ebert, C., Wright, F., Philippe, J.-C. & Pasqualini, J.R. (1999b) Effect of Medrogestone on  $17\beta$ -hydroxysteroid dehydrogenase activity in the hormone-dependent MCF-7 and T-47D human breast cancer cell lines. *J. steroid Biochem. mol. Biol.*, **68**, 51–56

- Chetrite, G.S., Thole, H.H., Philippe, J.-C. & Pasqualini, J.R. (2004) Dydrogesterone (Duphaston) and its 20-dihydro-derivative as selective estrogen enzyme modulators in human breast cancer cell lines. Effect on sulfatase and on 17 $\beta$ -hydroxysteroid dehydrogenase (17 $\beta$ -HSD) activity. *Anticancer Res.*, **24**, 1433–1438
- Chlebowski, R.T., Hendrix, S.L., Langer, R.D., Stefanick, M.L., Gass, M., Lane, D., Rodabough, R.J., Gilligan, M.A., Cyr, M.G., Thomson, C.A., Khandekar, J., Petrovich, H. & McTiernan, A. for the WHI Investigators (2003) Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: The Women's Health Initiative Randomized Trial. *J. Am. med. Assoc.*, **289**, 3243–3253
- Chlebowski, R.T., Wactawski-Wende, J., Ritenbaugh, C., Hubbell, F.A., Ascensao, J., Rodabough, R.J., Rosenberg, C.A., Taylor, V.M., Harris, R., Chen, C., Adams-Campbell, L.L. & White, E. for the Women's Health Initiative Investigators (2004) Estrogen plus progestin and colorectal cancer in postmenopausal women. *New Engl. J. Med.*, **350**, 991–1004
- Christodoulakos, G.E., Lambrinouadaki, I.V., Panoulis, K.P.C., Vourtsi, A.D., Vlachos, L., Georgiou, E. & Creatsas, G.C. (2003) The effect of various regimens of hormone replacement therapy on mammographic breast density. *Maturitas*, **45**, 109–118
- Cirillo, D.J., Wallace, R.B., Rodabough, R.J., Greenland, P., LaCroix, A.Z., Limacher, M.C. & Larson, J.C. (2005) Effect of estrogen therapy on gallbladder disease. *J. Am. med. Assoc.*, **293**, 330–339
- Civitelli, R., Pilgram, T.K., Dotson, M., Muckerman, J., Lewandowski, N., Armamento-Villareal, R., Yokoyama-Crothers, N., Kardaris, E.E., Hauser, J., Cohen, S. & Hildebolt, C.F. (2002) Alveolar and postcranial bone density in postmenopausal women receiving hormone/estrogen replacement therapy. A randomized, double-blind, placebo-controlled trial. *Arch. intern. Med.*, **162**, 1409–1415
- Clarkson, T.B., Anthony, M.S. & Jerome, C.P. (1998) Lack of effect of raloxifene on coronary artery atherosclerosis of postmenopausal monkeys. *J. clin. Endocrinol. Metab.*, **83**, 721–726
- Clarkson, T.B., Anthony, M.S. & Morgan, T.M. (2001) Inhibition of postmenopausal atherosclerosis progression: A comparison of the effects of conjugated equine estrogens and soy phytoestrogens. *J. clin. Endocrinol. Metab.*, **86**, 41–47
- Cline, J.M., Soderqvist, G., von Schoultz, E., Skoog, L. & von Schoultz, B. (1996) Effects of hormone replacement therapy on the mammary gland of surgically postmenopausal cynomolgus macaques. *Am. J. Obstet. Gynecol.*, **174**, 93–100
- Cline, J.M., Soderqvist, G., von Schoultz, E., Skoog, L. & von Schoultz, B. (1998) Effects of conjugated estrogens, medroxyprogesterone acetate, and tamoxifen on the mammary glands of macaques. *Breast Cancer Res. Treat.*, **48**, 221–229
- Cline, J.M., Register, T.C. & Clarkson, T.B. (2002a) Effects of tibolone and hormone replacement therapy on the breast of cynomolgus monkeys. *Menopause*, **9**, 422–429
- Cline, J.M., Register, T.C., & Clarkson, T.B. (2002b) Comparative effects of tibolone and conjugated equine estrogens with and without medroxyprogesterone acetate on the reproductive tract of female cynomolgus monkeys. *Menopause*, **9**, 242–252
- Colacurci, N., Fornaro, F., de Francis, P., Palermo, M. & del Vecchio, W. (2001) Effects of different types of hormone replacement therapy on mammographic density. *Maturitas*, **40**, 159–164
- Coldham, N.G. & James, V.H.T. (1990) A possible mechanism for increased breast cell proliferation by progestins through increased reductive 17 $\beta$ -hydroxysteroid dehydrogenase activity. *Int. J. Cancer*, **45**, 174–178

- Colditz, G.A., Willett, W.C., Stampfer, M.J., Rosner, B., Speizer, F.E. & Hennekens, C.H. (1987) Menopause and the risk of coronary heart disease in women. *New Engl. J. Med.*, **316**, 1105–1110
- Colditz, G.A., Egan, K.M. & Stampfer, M.J. (1993) Hormone replacement therapy and risk of breast cancer: Results from epidemiologic studies. *Am. J. Obstet. Gynecol.*, **168**, 1473–1480
- Collaborative Group on Hormonal Factors in Breast Cancer (1997) Breast cancer and hormone replacement therapy: Collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. *Lancet*, **350**, 1047–1059
- Collins, P., Rosano, G.M., Jiang, C., Lindsay, D., Sarrel, P.M. & Poole-Wilson, P.A. (1993) Cardiovascular protection by oestrogen — A calcium antagonist effect? *Lancet*, **341**, 1264–1265
- Collins, P., Rosano, G.M., Sarrel, P.M., Ulrich, L., Adamopoulos, S., Beale, C.M., McNeill, J.G. & Poole-Wilson, P.A. (1995)  $17\beta$ -Estradiol attenuates acetylcholine-induced coronary arterial constriction in women but not men with coronary heart disease. *Circulation*, **92**, 24–30
- Conner, P., Skoog, L. & Söderqvist, G. (2001) Breast epithelial proliferation in postmenopausal women evaluated through fine-needle-aspiration cytology. *Climacteric*, **4**, 7–12
- Conner, P., Söderqvist, G., Skoog, L., Gräser, T., Walter, F., Tani, E., Carlström, K. & von Schoultz, B. (2003) Breast cell proliferation in postmenopausal women during HRT evaluated through fine needle aspiration cytology. *Breast Cancer Res. Treat.*, **78**, 159–165
- Conner, P., Christow, A., Kersemaekers, W., Söderqvist, G., Skoog, L., Carlström, K., Tani, E., Mol-Arts, M. & von Schoultz, B. (2004a) A comparative study of breast cell proliferation during hormone replacement therapy: Effects of tibolon and continuous combined estrogen-progestogen treatment. *Climacteric*, **7**, 50–58
- Conner, P., Svane, G., Azavedo, E., Söderqvist, G., Carlström, K., Gräser, T., Walter, F. & von Schoultz, B. (2004b) Mammographic breast density, hormones and growth factors during continuous combined hormone therapy. *Fertil. Steril.*, **81**, 1617–1623
- Cooper, G.S., Dooley, M.A., Treadwell, E.L., St Clair, E.W. & Gilkeson, G.S. (2002) Hormonal and reproductive risk factors for development of systemic lupus erythematosus. *Arthritis. Rheum.*, **7**, 1830–1839
- Coughlin, S.S., Giustozzi, A., Smith, S.J. & Lee, N.C. (2000) A meta-analysis of estrogen replacement therapy and risk of epithelial ovarian cancer. *J. clin. Epidemiol.*, **53**, 367–375
- Couzinet, B., Young, J., Brailly, S., Chanson, P., Thomas, J.L. & Schaison, G. (1996) The antigonadotropic activity of progestins (19-nortestosterone and 19-norprogesterone derivatives) is not mediated through the androgen receptor. *J. clin. Endocrinol. Metab.*, **81**, 4218–4223
- Csizmadia, I., Collet, J.-P., Benedetti, A., Boivin, J.-F. & Hanley, J.A. (2004) The effects of transdermal and oral oestrogen replacement therapy on colorectal cancer risk in postmenopausal women. *Br. J. Cancer*, **90**, 76–81
- Currie, L.J., Harrison, M.B., Trugman, J.M., Bennett, J.P. & Wooten, F. (2004) Postmenopausal estrogen use affects risk for Parkinson disease. *Arch. Neurol.*, **61**, 886–888
- Cushman, M., Legault, C., Barrett-Connor, E., Stefanick, M.L., Kessler, C., Judd, H.L., Sakkinen, P.A. & Tracy, R.P. (1999) Effect of postmenopausal hormones on inflammation-sensitive proteins: The Postmenopausal Estrogen/Progestin Interventions (PEPI) Study. *Circulation*, **100**, 717–722
- Cushman, M., Kuller, L.H., Prentice, R., Rodabough, R.J., Psaty, B.M., Stafford, R.S., Sidney, S. & Rosendaal, F.R. (2004) Estrogen plus progestin and risk of venous thrombosis. *J. Am. med. Assoc.*, **292**, 1573–1580



- Dahmoun, M., Ödmark, I.-S., Risberg, B., Karlsson, M.G., Pavlenko, T. & Backstrom, T. (2004) Apoptosis, proliferation, and sex steroid receptors in postmenopausal endometrium before and during HRT. *Maturitas*, **49**, 114–123
- Daling, J.R., Malone, K.E., Doody, D.R., Voigt, L.F., Bernstein, L., Coates, R.J., Marchbanks, P.A., Norman, S.A., Weiss, L.K., Ursin, G., Berlin, J.A., Burkman, R.T., Deapen, D., Folger, S.G., McDonald, J.A., Simon, M.S., Strom, B.L., Wingo, P.A. & Spirtas, R. (2002) Relation of regimens of combined hormone replacement therapy to lobular, ductal, and other histologic types of breast carcinoma. *Cancer*, **95**, 2455–2464
- Davis, S.R., Dinatale, I., Rivera-Woll, L. & Davison, S. (2005) Postmenopausal hormone therapy: From monkey glands to transdermal patches. *J. Endocrinol.*, **185**, 207–222
- Dawling, S., Roodi, N., Mernaugh, R.L., Wang, X. & Parl, F.F. (2001) Catechol-*O*-methyltransferase (COMT)-mediated metabolism of catechol estrogens: Comparison of wild-type and variant COMT isoforms. *Cancer Res.*, **61**, 6716–6722
- Dawling, S., Roodi, N. & Parl, F.F. (2003) Methoxyestrogens exert feedback inhibition on cytochrome P450 1A1 and 1B1. *Cancer Res.*, **63**, 3127–3132
- Dawling, S., Hachey, D.L., Roodi, N. & Parl, F.F. (2004) In vitro model of mammary estrogen metabolism: Structural and kinetic differences between catechol estrogens 2- and 4-hydroxyestradiol. *Chem. Res. Toxicol.*, **17**, 1258–1264
- Deckers, G.H., Schoonen, W.G.E.J. & Kloosterboer, H.J. (2000) Influence of the substitution of 11-methylene, delta<sup>15</sup>, and/or 18-methyl groups in norethisterone on receptor binding, transactivation assays and biological activities in animals. *J. steroid Biochem. mol. Biol.*, **74**, 83–92
- Devanesan, P., Santen, R.J., Bocchinfuso, W.P., Korach, K.S., Rogan, E.G. & Cavalieri, E. (2001) Catechol estrogen metabolites and conjugates in mammary tumors and hyperplastic tissue from estrogen receptor- $\alpha$  knock-out (ERKO)/Wnt-1 mice: Implications for initiation of mammary tumors. *Carcinogenesis*, **22**, 1573–1576
- De Vivo, I., Hankinson, S.E., Li, L., Colditz, G.A. & Hunter, D.J. (2002) Association of *CYP1B1* polymorphisms and breast cancer risk. *Cancer Epidemiol. Biomarkers Prev.*, **11**, 489–492
- Dijkema, R., Schoonen, W.G.E.J., Teuwen, R., van der Struik, S.E., de Ries, R.J.H., van der Kar, B.A.T. & Olijve, W. (1998) Human progesterone receptor A and B isoforms in CHO cells. I. Stable transfection of receptor and receptor-responsive reporter genes: Transcription modulation by (anti)progestagens. *J. steroid Biochem. mol. Biol.*, **64**, 147–156
- Donker, G.A., Spreeuwenberg, P., Bartelds, A.I.M., van der Velden, K. & Foets, M. (2000) Hormone replacement therapy: Changes in frequency and type of prescription by Dutch GPs during the last decade of the millennium. *Fam. Pract.*, **17**, 508–513
- Dören, M., Rübiger, A., Coelingh Bennink, H.J.T. & Holzgreve, W. (2001) Differential effects on the androgen status of postmenopausal women treated with tibolone and continuous combined estradiol and norethindrone acetate replacement therapy. *Fertil. Steril.*, **75**, 554–559
- Ekström, H., Esseveld, J. & Hovellius, B. (2003) Associations between attitudes toward hormone therapy and current use of it in middle-aged women. *Maturitas*, **46**, 45–57
- d'Elia, H.F., Larsen, A., Mattsson, L.-A., Waltbrand, E., Kvist, G., Mellström, D., Saxne, T., Ohlsson, C., Nordborg, E. & Carlsten, H. (2003) Influence of hormone replacement therapy on disease progression and bone mineral density in rheumatoid arthritis. *J. Rheumatol.* **30**, 1456–1463
- El-Rayes, B.F., Ali, S., Heilbrun, L.K., Lababidi, S., Bouwman, D., Visscher, D. & Philip, P.A. (2003) Cytochrome P450 and glutathione transferase expression in human breast cancer. *Clin. Cancer Res.*, **9**, 1705–1709

- Embrechts, J., Lemiere, F., Van Dongen, W., Esmans, E.L., Buytaert, P., Van Marck, E., Kockx, M. & Makar, A. (2003) Detection of estrogen DNA-adducts in human breast tumor tissue and healthy tissue by combined nano LC-nano ES tandem mass spectrometry. *J. Am. Soc. mass Spectrom.*, **14**, 482–491
- Erel, C.T., Esen, G., Seyisoglu, H., Elter, K., Uras, C., Ertungealp, E. & Aksu, M.F. (2001) Mammographic density increase in women receiving different hormone replacement regimens. *Maturitas*, **40**, 151–157
- Espeland, M.A., Applegate, W., Furberg, C.D., Lefkowitz, D., Rice, L. & Hunninghake, D. for the ACAPS Investigators (1995a) Estrogen replacement therapy and progression of intimal-medial thickness in the carotid arteries of postmenopausal women. *Am. J. Epidemiol.*, **142**, 1011–1019
- Espeland, M.A., Bush, T.L., Mebane-Sims, I., Stefanick, M.L., Johnson, S., Sherwin, R. & Waclawiw, M. for the PEPI Trial Investigators (1995b) Rationale, design, and conduct of the PEPI Trial. *Control. clin. Trials*, **16**, 3S–19S
- Espeland, M.A., Rapp, S.R., Shumaker, S.A., Brunner, R., Manson, J.E., Sherwin, B.B., Hsia, J., Margolis, K.L., Hogan, P.E., Wallace, R., Dailey, M., Freeman, R. & Hays, J. for the Women's Health Initiative Memory Study Investigators (2004) Conjugated equine estrogens and global cognitive function in postmenopausal women. Women's Health Initiative Memory Study. *J. Am. med. Assoc.*, **291**, 2959–2968
- Ewertz, M., Mellekjaer, L., Poulsen, A.H., Friis, S., Sorensen, H.T., Pedersen, L., McLaughlin, J.K. & Olsen, J.H. (2005) Hormone use for menopausal symptoms and risk of breast cancer. A Danish cohort study. *Br. J. Cancer*, **92**, 1293–1297
- Facchinetti, F., Nappi, R.E., Tirelli, A., Polatti, F. & Nappi, G. (2002) Hormone supplementation differently affects migraine in postmenopausal women. *Headache*, **42**, 924–929
- Falany, C.N., Xie, X., Wang, J., Ferrer, J. & Falany, J.L. (2000) Molecular cloning and expression of novel sulphotransferase-like cDNAs from human and rat brain. *Biochem. J.*, **346**, 857–864
- Falany, J.L., Macrina, N. & Falany, C.N. (2002) Regulation of MCF-7 breast cancer cell growth by  $\beta$ -estradiol sulfation. *Breast Cancer Res. Treat.*, **74**, 167–176
- Falk, R.T., Rossi, S.C., Fears, T.R., Sepkovic, D.W., Migella, A., Adlercreutz, H., Donaldson, J., Bradlow, H.L. & Ziegler, R.G. (2000) A new ELISA kit for measuring urinary 2-hydroxyestrone, 16 $\alpha$ -hydroxyestrone, and their ratio: Reproducibility, validity, and assay performance after freeze-thaw cycling and preservation by boric acid. *Cancer Epidemiol. Biomarkers Prev.*, **9**, 81–87
- Fantl, J.A., Bump, R.C., Robinson, D., McClish, D.K., Wyman, J.R. & the Continence Program for Women Research Group (1996) Efficacy of estrogen supplementation in the treatment of urinary incontinence. *Obstet. Gynecol.*, **88**, 745–749
- Faucher, F., Lacoste, L., Dufort, I. & Luu-The, V. (2001) High metabolism of catecholestrogens by type 1 estrogen sulfotransferase (hEST1). *J. steroid Biochem. mol. Biol.*, **77**, 83–86
- Feigelson, H.S., McKean-Cowdin, R., Coetzee, G.A., Stram, D.O., Kolonel, L.N. & Henderson, B.E. (2001) Building a multigenic model of breast cancer susceptibility: *CYP17* and *HSD17B1* are two important candidates. *Cancer Res.*, **61**, 785–789
- Felty, Q. & Roy, D. (2005a) Mitochondrial signals to nucleus regulate estrogen-induced cell growth. *Med. Hypotheses*, **64**, 133–141
- Felty, Q. & Roy, D. (2005b) Estrogen, mitochondria, and growth of cancer and non-cancer cells. *J. Carcinog.*, **4**, 1

- Felty, Q., Singh, K.P. & Roy, D. (2005a) Estrogen-induced G<sub>1</sub>/S transition of G<sub>0</sub>-arrested estrogen-dependent breast cancer cells is regulated by mitochondrial oxidant signaling. *Oncogene*, **24**, 4883–4893
- Felty, Q., Xiong, W.-C., Sun, D., Sarkar, S., Singh, K.P., Parkash, J. & Roy, D. (2005b) Estrogen-induced mitochondrial reactive oxygen species as signal-transducing messengers. *Biochemistry*, **44**, 6900–6909
- Ferenczy, A. & Gelfand, M.M. (1997) Endometrial histology and bleeding patterns in post-menopausal women taking sequential, combined estradiol and dydrogesterone. *Maturitas*, **26**, 219–226
- Fernandez, S.V., Russo, I.H., Lareef, M., Balsara, B. & Russo, J. (2005) Comparative genomic hybridization of human breast epithelial cells transformed by estrogen and its metabolites. *Int. J. Oncol.*, **26**, 691–695
- Fournier, A., Berrino, F., Riboli, E., Avenel, V. & Clavel-Chapelon, F. (2005) Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. *Int. J. Cancer*, **114**, 448–454
- Franke, H.R. & Vermes, I. (2002) The effect of continuous combined 17 $\beta$ -oestradiol and dihydrodydrogesterone on apoptotic cell death and proliferation of human breast cancer cells in vitro. *Eur. J. Cancer*, **38** (Suppl.), S69–S70
- Franke, H.R. & Vermes, I. (2003) Differential effects of progestogens on breast cancer cell lines. *Maturitas*, **46** (Suppl. 1), S55–S58
- Franke, H.R., Kole, S., Ciftci, Z., Haanen, C. & Vermes, I. (2003) In vitro effects of estradiol, dydrogesterone, tamoxifen and cyclophosphamide on proliferation vs. death in human breast cancer cells. *Cancer Lett.*, **190**, 113–118
- Freedman, M., San Martin, J., O’Gorman, J., Eckert, S., Lippman, M.E., Lo, S.-C.B., Walls, E.L. & Zeng, J. (2001) Digitized mammography: A clinical trial of postmenopausal women randomly assigned to receive raloxifene, estrogen, or placebo. *J. natl Cancer Inst.*, **93**, 51–56
- Freeman, E.E., Munoz, B., Schein, O.D. & West, S.K. (2004) Incidence and progression of lens opacities. Effect of hormone replacement therapy and reproductive factors. *Epidemiology*, **15**, 451–457
- Fugère, P., Scheele, W.H., Shah, A., Strack, T.R., Glant, M.D. & Jolly, E. (2000) Uterine effects of raloxifene in comparison with continuous–combined hormone replacement therapy in postmenopausal women. *Am. J. Obstet. Gynecol.*, **182**, 568–574
- Gabriel-Sánchez, R., Carmona, L., Roque, M., Sánchez-Gómez, L.M. & Bonfill, X. (2005) Hormone replacement therapy for preventing cardiovascular disease in post-menopausal women. *Cochrane Database. Syst. Rev.*, CD002229
- Gall, W.E., Zawada, G., Mojarrabi, B., Tephly, T.R., Green, M.D., Coffman, B.L., Mackenzie, P.I. & Radominska-Pandya, A. (1999) Differential glucuronidation of bile acids, androgens and estrogens by human UGT1A3 and 2B7. *J. steroid Biochem. mol. Biol.*, **70**, 101–108
- Gambacciani, M., Monteleone, P., Vitale, C., Silvestri, A., Fini, M., Genazzani, A.R. & Rosano, G.M.C. (2002) Dydrogesterone does not reverse the effects of estradiol on endothelium-dependant vasodilation in postmenopausal women: A randomized clinical trial. *Maturitas*, **43**, 117–123
- Gambrell, R.D. (1986) Prevention of endometrial cancer with progestogens. *Maturitas*, **8**, 159–168

- García-Becerra, R., Cooney, A.J., Borja-Cacho, E., Lemus, A.E., Pérez-Palacios, G. & Larrea, F. (2004) Comparative evaluation of androgen and progesterone receptor transcription selectivity indices of 19-nortestosterone-derived progestins. *J. steroid Biochem. mol. Biol.*, **91**, 21–27
- Garg, P.P., Kerlikowske, K., Subak, L. & Grady, D. (1998) Hormone replacement therapy and the risk of epithelial ovarian carcinoma: A meta-analysis. *Obstet. Gynecol.*, **92**, 472–479
- Garte, S., Gaspari, L., Alexandrie, A.K., Ambrosone, C., Autrup, H., Autrup, J.L., Baranova, H., Bathum, L., Benhamou, S., Boffetta, P., Bouchardy, C., Breskvar, K., Brockmoller, J., Cascorbi, I., Clapper, M.L., Coutelle, C., Daly, A., Dell’Omo, M., Dolzan, V., Dresler, C.M., Fryer, A., Haugen, A., Hein, D.W., Hildesheim, A., Hirvonen, A., Hsieh, L.-L., Ingelman-Sundberg, M., Kalina, I., Kang, D., Kihara, M., Kiyohara, C., Kremers, P., Lazarus, P., Le Marchand, L., Lechner, M.C., van Lieshout, E.M.M., London, S., Manni, J.J., Maugard, C.M., Morita, S., Nazar-Stewart, V., Noda, K., Oda, Y., Parl, F.F., Pastorelli, R., Persson, I., Peters, W.H.M., Rannug, A., Rebbeck, T., Risch, A., Roelandt, L., Romkes, M., Ryberg, D., Salagovic, J., Schoket, B., Seidegard, J., Shields, P.G., Sim, E., Sinnet, D., Strange, R.C., Stücker, I., Sugimura, H., To-Figueras, J., Vineis, P., Yu, M.C. & Taioli, E. (2001) Metabolic gene polymorphism frequencies in control populations. *Cancer Epidemiol. Biomarkers Prev.*, **10**, 1239–1248
- Georgiev, D.B. & Manassiev, N.A. (2002) Effect of long-term continuous combined hormone replacement therapy with estradiol valerate and either dienogest or norethisterone acetate on mammographic density in postmenopausal women. *Medscape Womens Health*, **7**, 1
- Gestl, S.A., Green, M.D., Shearer, D.A., Frauenhoffer, E., Tephly, T.R. & Weisz, J. (2002) Expression of UGT2B7, a UDP-glucuronosyltransferase implicated in the metabolism of 4-hydroxyestrone and all-*trans* retinoic acid, in normal human breast parenchyma and in invasive and *in situ* breast cancers. *Am. J. Pathol.*, **160**, 1467–1479
- Gilligan, D.M., Quyyumi, A.A. & Cannon, R.O., III (1994a) Effects of physiological levels of estrogen on coronary vasomotor function in postmenopausal women. *Circulation*, **89**, 2545–2551
- Gilligan, D.M., Badar, D.M., Panza, J.A., Quyyumi, A.A. & Cannon, R.O., III (1994b) Acute vascular effects of estrogen in postmenopausal women. *Circulation*, **90**, 786–791
- Glatt, H., Engelke, C.E., Pabel, U., Teubner, W., Jones, A.L., Coughtrie, M.W., Andrae, U., Falany, C.N. & Meinel, W. (2000) Sulfotransferases: Genetics and role in toxicology. *Toxicol. Lett.*, **112–113**, 341–348
- Glud, E., Kjaer, S.K., Thomsen, B.L., Hogdall, C., Christensen, L., Hogdall, E., Bock, J.E. & Blaakaer, J. (2004) Hormone therapy and the impact of estrogen intake on the risk of ovarian cancer. *Arch. intern. Med.*, **164**, 2253–2259
- Goldstein, S.R., Johnson, S., Watts, N.B., Ciaccia, A.V., Elmerick, D. & Muram, D. (2005) Incidence of urinary incontinence in postmenopausal women treated with raloxifene or estrogen. *Menopause*, **12**, 160–164
- Goodman, M.T., McDuffie, K., Kolonel, L.N., Terada, K., Donlon, T.A., Wilkens, L.R., Guo, C. & Le Marchand, L. (2001) Case-control study of ovarian cancer and polymorphisms in genes involved in catecholesterogen formation and metabolism. *Cancer Epidemiol. Biomarkers Prev.*, **10**, 209–216
- Goodman, J.E., Lavigne, J.A., Wu, K., Helzlsouer, K.J., Strickland, P.T., Selhub, J. & Yager, J.D. (2001) *COMT* genotype, micronutrients in the folate metabolic pathway and breast cancer risk. *Carcinogenesis*, **22**, 1661–1665

- Goodman, J.E., Jensen, L.T., He, P. & Yager, J.D. (2002) Characterization of human soluble high and low activity catechol-*O*-methyltransferase catalyzed catechol estrogen methylation. *Pharmacogenetics*, **12**, 517–528
- Gordon, T., Kannel, W.B., Hjortland, M.C. & McNamara, P.M. (1978) Menopause and coronary heart disease. The Framingham Study. *Ann. intern. Med.*, **89**, 157–161
- Goth-Goldstein, R., Stampfer, M.R., Erdmann, C.A. & Russell, M. (2000) Interindividual variation in *CYP1A1* expression in breast tissue and the role of genetic polymorphism. *Carcinogenesis*, **21**, 2119–2122
- Grady, D., Rubin, S.M., Petitti, D.B., Fox, C.S., Black, D., Ettinger, B., Ernster, V.L. & Cummings, S.R. (1992) Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann. intern. Med.*, **117**, 1016–1037
- Grady, D., Applegate, W., Bush, T., Furberg, C., Riggs, B. & Hulley, S.B., for the HERS Research Group (1998) Heart and Estrogen/Progestin Replacement Study (HERS): Design, methods, and baseline characteristics. *Control. clin. Trials*, **19**, 314–335
- Grady, D., Brown, J.S., Vittinghoff, E., Applegate, W., Varner, E. & Snyder, T. for the HERS Research Group (2001) Postmenopausal hormones and incontinence: The Heart and Estrogen/Progestin Replacement Study. *Obstet. Gynecol.*, **97**, 116–120
- Grady, D., Herrington, D., Bittner, V., Blumenthal, R., Davidson, M., Hlatky, M., Hsia, J., Hulley, S., Herd, A., Khan, S., Newby, L.K., Waters, D., Vittinghoff, E. & Wenger, N. for the HERS Research Group (2002a) Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/Progestin Replacement Study follow-up (HERS II). *J. Am. med. Assoc.*, **288**, 49–57
- Grady, D., Yaffe, K., Kristof, M., Lin, F., Richards, C. & Barrett-Connor, E. (2002b) Effect of postmenopausal hormone therapy on cognitive function: The Heart and Estrogen/progestin Replacement Study. *Am. J. Med.*, **113**, 543–548
- Greendale, G.A., Reboussin, B.A., Hogan, P., Barnabei, V.M., Shumaker, S., Johnson, S. & Barrett-Connor, E. for the Postmenopausal Estrogen/Progestin Interventions Trial Investigators (1998) Symptom relief and side effects of postmenopausal hormones: Results from the Postmenopausal Estrogen/Progestin Interventions Trial. *Obstet. Gynecol.*, **92**, 982–988
- Greendale, G.A., Lee, N.P. & Arriola, E.R. (1999) The menopause. *Lancet*, **353**, 571–580
- Greendale, G.A., Reboussin, B.A., Slone, S., Wasilauskas, C., Pike, M.C. & Ursin, G. (2003) Postmenopausal hormone therapy and change in mammographic density. *J. natl Cancer Inst.*, **95**, 30–37
- Grodstein, F., Manson, J.E., Colditz, G.A., Willett, W.C., Speizer, F.E. & Stampfer, M.J. (2000) A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. *Ann. intern. Med.*, **133**, 933–941
- Grundy, S.M., Pasternak, R., Greenland, P., Smith, S. & Fuster, V. (1999) Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations: A statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *J. Am. Coll. Cardiol.*, **34**, 1348–1359
- Guillemette, C., Millikan, R.C., Newman, B. & Housman, D.E. (2000) Genetic polymorphisms in uridine diphospho-glucuronosyltransferase 1A1 and association with breast cancer among African Americans. *Cancer Res.*, **60**, 950–956

- Guillemette, C., De Vivo, I., Hankinson, S.E., Haiman, C.A., Spiegelman, D., Housman, D.E. & Hunter, D.J. (2001) Association of genetic polymorphisms in UGT1A1 with breast cancer and plasma hormone levels. *Cancer Epidemiol. Biomarkers Prev.*, **10**, 711–714
- Gunnarsson, C., Olsson, B.M. & Stål, O. (2001) Abnormal expression of 17 $\beta$ -hydroxysteroid dehydrogenases in breast cancer predicts late recurrence. *Cancer Res.*, **61**, 8448–8451
- Gunnarsson, C., Ahnström, M., Kirschner, K., Olsson, B., Nordenskjöld, B., Rutqvist, L.E., Skoog, L. & Stål, O. (2003) Amplification of *HSD17B1* and *ERBB2* in primary breast cancer. *Oncogene*, **22**, 34–40
- Haas, J.S., Kaplan, C.P., Gerstenberger, E.P. & Kerlikowske, K. (2004) Changes in the use of postmenopausal hormone therapy after the publication of clinical trial results. *Ann. intern. Med.*, **140**, 184–188
- Habiba, M.A., Bell, S.C. & Al-Azzawi, F. (1998) Endometrial responses to hormone replacement therapy: Histological features compared with those of late luteal phase endometrium. *Hum. Reprod.*, **13**, 1674–1682
- Hachey, D.L., Dawling, S., Roodi, N. & Parl, F.F. (2003) Sequential action of phase I and II enzymes cytochrome P450 1B1 and glutathione S-transferase P1 in mammary estrogen metabolism. *Cancer Res.*, **63**, 8492–8499
- Hammond, C.B., Jelovsek, F.R., Lee, K.L., Creasman, W.T. & Parker, R.T. (1979) Effects of long-term estrogen replacement therapy. II. Neoplasia. *Am. J. Obstet. Gynecol.*, **133**, 537–547
- Hänggi, W., Bersinger, N., Altermatt, H.J. & Birkhäuser, M.H. (1997) Comparison of transvaginal ultrasonography and endometrial biopsy in endometrial surveillance in postmenopausal HRT users. *Maturitas*, **27**, 133–143
- Hanna, I.H., Dawling, S., Roodi, N., Guengerich, F.P. & Parl, F.F. (2000) Cytochrome P450 *1B1* (*CYP1B1*) pharmacogenetics: Association of polymorphisms with functional differences in estrogen hydroxylation activity. *Cancer Res.*, **60**, 3440–3444
- Hannaford, P. & Elliot, A. (2005) Use of exogenous hormones by women and colorectal cancer: Evidence from the Royal College of General Practitioners' Oral Contraception Study. *Contraception*, **71**, 95–98
- Hargreaves, D.F., Knox, F., Swindell, R., Potten, C.S. & Bundred, N.J. (1998) Epithelial proliferation and hormone receptor status in the normal post-menopausal breast and the effects of hormone replacement therapy. *Br. J. Cancer*, **78**, 945–949
- Hays, J., Ockene, J.K., Brunner, R.L., Kotchen, J.M., Manson, J.E., Patterson, R.E., Aragaki, A.K., Shumaker, S.A., Brzyski, R.G., LaCroix, A.Z., Granek, I.A. & Valanis, B.G. for the Women's Health Initiative Investigators (2003a) Effects of estrogen plus progestin on health-related quality of life. *New Engl. J. Med.*, **348**, 1839–1854
- Hays, J., Hunt, J.R., Hubbell, F.A., Anderson, G.L., Limacher, M., Allen, C. & Rossouw, J.E. (2003b) The Women's Health Initiative recruitment methods and results. *Ann. Epidemiol.*, **13**, S18–S77
- Heald, A., Selby, P.L., White, A. & Gibson, J.M. (2000) Progestins abrogate estrogen-induced changes in the insulin-like growth factor axis. *Am. J. Obstet. Gynecol.*, **183**, 593–600
- Henderson, V.W., Paganini-Hill, A., Miller, B.L., Elble, R.J., Reyes, P.F., Shoupe, D., McCleary, C.A., Klein, R.A., Hake, A.M. & Farlow, M.R. (2000) Estrogen for Alzheimer's disease in women: Randomized, double-blind, placebo-controlled trial. *Neurology*, **54**, 295–301

- Hendrix, S.L., Cochrane, B.B., Nygaard, I.E., Handa, V.L., Barnabei, V.M., Iglesia, C., Aragaki, A., Naughton, M.J., Wallace, R.B. & McNealey, S.G. (2005) Effects of estrogen with and without progestin on urinary incontinence. *J. Am. med. Assoc.*, **293**, 935–948
- Heng, D., Gao, F., Jong, R., Fishell, E., Yaffe, M., Martin, L., Li, T., Stone, J., Sun, L., & Hopper, J. (2004) Risk factors for breast cancer associated with mammographic features in Singaporean chinese women. *Cancer Epidemiol. Biomarkers Prev.*, **13**, 1751–1758
- Herrington, D.M., Braden, G.A., Williams, J.K. & Morgan, T.M. (1994) Endothelial-dependent coronary vasomotor responsiveness in postmenopausal women with and without estrogen replacement therapy. *Am. J. Cardiol.*, **73**, 951–952
- Herrington, D.M., Reboussin, D.M., Brosnihan, K.B., Sharp, P.C., Shumaker, S.A., Snyder, T.E., Furberg, C.D., Kowalchuk, G.J., Stuckey, T.D., Rogers, W.J., Givens, D.H. & Waters, D. (2000) Effects of estrogen replacement on the progression of coronary–artery atherosclerosis. *New Engl. J. Med.*, **343**, 522–529
- Herrington, D.M., Espeland, M.A., Crouse, J.R., III, Robertson, J., Riley, W.A., McBurnie, M.A. & Burke, G.L. (2001) Estrogen replacement and brachial artery flow-mediated vasodilation in older women. *Arterioscler. Thromb. vasc. Biol.*, **21**, 1955–1961
- Hersh, A.L., Stefanick, M.L. & Stafford, R.S. (2004) National use of postmenopausal hormone therapy: Annual trends and response to recent evidence. *J. Am. med. Assoc.*, **291**, 47–53
- Hill, D.A., Weiss, N.S., Beresford, S.A., Voigt, L.F., Daling, J.R., Stanford, J.L. & Self, S. (2000) Continuous combined hormone replacement therapy and risk of endometrial cancer. *Am. J. Obstet. Gynecol.*, **183**, 1456–1461
- Hirvonen, E. (1996) Progestins. *Maturitas*, **23** (Suppl.), S13–S18
- Hlatky, M.A., Boothroyd, D., Vittinghoff, E., Sharp, P. & Whooley, M.A. for the HERS Research Group (2002) Quality-of-life and depressive symptoms in postmenopausal women after receiving hormone therapy. Results from the Heart and Estrogen/Progestin Replacement Study (HERS) Trial. *J. Am. med. Assoc.*, **287**, 591–597
- Ho, G.H., Luo, X.W., Ji, C.Y., Foo, S.C. & Ng E.H. (1998) Urinary 2/16 $\alpha$ -hydroxyestrone ratio: Correlation with serum insulin-like growth factor binding protein-3 and a potential biomarker of breast cancer risk. *Ann. Acad. Med. Singapore*, **27**, 294–299
- Hochberg, R.B. (1998) Biological esterification of steroids. *Endocr. Rev.*, **19**, 331–348
- Hodis, H.N., Mack, W.J., Lobo, R.A., Shoupe, D., Sevanian, A., Mahrer, P.R., Selzer, R.H., Liu, C.-R., Liu, C.-H. & Azen, S.P. (2001) Estrogen in the prevention of atherosclerosis. A randomized, double-blind, placebo-controlled trial. *Ann. intern. Med.*, **135**, 939–953
- Hoffmann, H., Hillesheim, H.G., Güttner, J., Stade, K., Merbt, E.-M., Holle, K., Oettel, M., Strecke, J., Hesse, G., Horn, U., Valentin, U., Lemke, H., Chemnitius, K.H., Schimmel, I., Deufrains, J., Hesse, V., Keil, E., Klinger, G., Klinger, G., Stelzner, A., Furcht, R., Gaida, P., Anke, M., Dettmann, R., Kramp, B. & Robiller, F. (1983) Long term toxicological studies on the progestin STS 557. *Exp. clin. Endocrinol.*, **81**, 179–196
- Hofling, M., Carlström, K., Svane, G., Azavedo, E., Kloosterboer, H. & von Schoultz, B. (2005) Different effects of tibolone and continuous combined estrogen plus progestogen hormone therapy on sex hormone binding globulin and free testosterone levels—An association with mammographic density. *Gynecol. Endocrinol.*, **20**, 110–115
- Hofseth, L.J., Raafat, A.M., Osuch, J.R., Pathak, D.R., Slomski, C.A. & Haslam, S.Z. (1999) Hormone replacement therapy with estrogen or estrogen plus medroxyprogesterone acetate is

- associated with increased epithelial proliferation in the normal postmenopausal breast. *J. clin. Endocrinol. Metab.*, **84**, 4559–4565
- Hong, C.-C., Thompson, H.J., Jiang, C., Hammond, G.L., Trichtler, D., Yaffe, M. & Boyd, N.F. (2003) Val158Met polymorphism in *catechol-O-methyltransferase* gene associated with risk factors for breast cancer. *Cancer Epidemiol. Biomarkers Prev.*, **12**, 838–847
- Hoover, R., Gray, L.A., Sr, Cole, P. & MacMahon, B. (1976) Menopausal estrogens and breast cancer. *New Engl. J. Med.*, **295**, 401–405
- Horwitz, K.B. & Horwitz, L.D. (1982) Canine vascular tissues are targets for androgens, estrogens, progestins, and glucocorticoids. *J. clin. Invest.*, **69**, 750–758
- Hu, X., Xia, H., Srivastava, S.K., Herzog, C., Awasthi, Y.C., Ji, X., Zimniak, P. & Singh, S.V. (1997) Activity of four allelic forms of glutathione S-transferase hGSTP1-1 for diol epoxides of polycyclic aromatic hydrocarbons. *Biochem. biophys. Res. Commun.*, **238**, 397–402
- Huang, C.-S., Shen, C.-Y., Chang, K.-J., Hsu, S.-M. & Chern, H.-D. (1999) Cytochrome P4501A1 polymorphism as a susceptibility factor for breast cancer in postmenopausal Chinese women in Taiwan. *Br. J. Cancer*, **80**, 1838–1843
- Huang, P., Feng, L., Oldham, E.A., Keating, M.J. & Plunkett, W. (2000) Superoxide dismutase as a target for the selective killing of cancer cells. *Nature*, **407**, 390–395
- Huang, Y.H., Galijatovic, A., Nguyen, N., Geske, D., Beaton, D., Green, J., Green, M., Peters, W.H. & Tukey, R.H. (2002) Identification and functional characterization of UDP-glucuronosyltransferases UGT1A8\*1, UGT1A8\*2 and UGT1A8\*3. *Pharmacogenetics*, **12**, 287–297
- Hulley, S., Furberg, C., Barrett-Connor, E., Cauley, J., Grady, D., Haskell, W., Knopp, R., Lowery, M., Satterfield, S., Schrott, H., Vittinghoff, E. & Hunninghake, D. for the HERS Research Group (2002) Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/Progestin Replacement Study follow-up (HERS II). *J. Am. med. Assoc.*, **288**, 58–66
- Hulley, S., Grady, D., Bush, T., Furberg, C., Herrington, D., Riggs, B. & Vittinghoff, E. (1998) Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/Progestin Replacement Study (HERS) Research Group. *J. Am. med. Assoc.*, **280**, 605–613
- Hundal, B.S., Dhillon, V.S. & Sidhu, I.S. (1997) Genotoxic potential of estrogens. *Mutat. Res.*, **389**, 173–181
- Hurh, Y.-J., Chen, Z.-H., Na, H.-K., Han, S.-Y. & Surh, Y.-J. (2004) 2-Hydroxyestradiol induces oxidative DNA damage and apoptosis in human mammary epithelial cells. *J. Toxicol. environ Health*, **A67**, 1939–1953
- IARC (1979) *IARC Monographs on the Evaluation of the Carcinogenic Risks of Chemicals to Humans*, Vol. 21, *Sex Hormones (II)*, Lyon
- IARC (1999) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 72, *Hormonal Contraception and Post-menopausal Hormonal Therapy*, Lyon
- IARC (2007) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 90, *Human Papillomaviruses*, Lyon
- Iatrakis, G., Tsonis, C., Antoniadis, S. & Kourounis, G. (2004) Effect on endometrium of combined oestrogen-progestogen replacement therapy of 1 mg 17 $\beta$ -estradiol and 0.5 mg norethisterone acetate. *Clin. exp. Obstet. Gynecol.*, **31**, 50–52
- IMS Health (2005) *IMS Health MIDAS*, June



- Isaksson, E., Wang, H., Sahlin, L., von Schoultz, B., Cline, J.M. & von Schoultz, E. (2003) Effects of long-term HRT and tamoxifen on the expression of progesterone receptors A and B in breast tissue from surgically postmenopausal cynomolgus macaques. *Breast Cancer Res. Treat.*, **79**, 233–239
- Jackson, S., Shepherd, A., Brookes, S. & Abrams, P. (1999) The effect of oestrogen supplementation on post-menopausal urinary stress incontinence: A double-blind placebo-controlled trial. *Br. J. Obstet. Gynaecol.*, **106**, 711–718
- Jacobs, E.J., White, E., Weiss, N.S., Heckbert, S.R., LaCroix, A. & Barlow, W.E. (1999) Hormone replacement therapy and colon cancer among members of a health maintenance organization. *Epidemiology*, **10**, 445–451
- Jain, M.G., Rohan, T.E. & Howe, G.R. (2000) Hormone replacement therapy and endometrial cancer in Ontario, Canada. *J. clin. Epidemiol.*, **53**, 385–391
- Jefcoate, C.R., Liehr, J.G., Santen, R.J., Sutter, T.R., Yager, J.D., Yue, W., Santner, S.J., Tekmal, R., Demers, L., Pauley, R., Naftolin, F., Mor, G. & Berstein, L. (2000) Tissue-specific synthesis and oxidative metabolism of estrogens. *J. natl Cancer Inst. Monogr.*, **27**, 95–112
- Jernström, H., Bendahl, P.O., Lidfeldt, J., Nerbrand, C., Agardh, C.D. & Samsioe, G. (2003a) A prospective study of different types of hormone replacement therapy use and the risk of subsequent breast cancer: The Women's Health in the Lund Area (WHILA) study (Sweden). *Cancer Causes Control*, **14**, 673–680
- Jernström, H., Klug, T.L., Sepkovic, D.W., Bradlow, H.L. & Narod, S.A. (2003b) Predictors of the plasma ratio of 2-hydroxyestrone to 16 $\alpha$ -hydroxyestrone among pre-menopausal, nulliparous women from four ethnic groups. *Carcinogenesis*, **24**, 991–1005
- Ji, X., Blaszczyk, J., Xiao, B., O'Donnell, R., Hu, X., Herzog, C., Singh, S.V. & Zimniak, P. (1999) Structure and function of residue 104 and water molecules in the xenobiotic substrate-binding site in human glutathione S-transferase P1-1. *Biochemistry*, **38**, 10231–10238
- Jiang, C., Sarrel, P.M., Lindsay, D.C., Poole-Wilson, P.A. & Collins, P. (1991) Endothelium-independent relaxation of rabbit coronary artery by 17  $\beta$ -oestradiol *in vitro*. *Br J Pharmacol.*, **104**, 1033–1037
- Jiang, C., Poole-Wilson, P.A., Sarrel, P.M., Mochizuki, S., Collins, P. & MacLeod, K.T. (1992a) Effect of 17 $\beta$ -oestradiol on contraction, Ca<sup>2+</sup> current and intracellular free Ca<sup>2+</sup> in guinea-pig isolated cardiac myocytes. *Br. J. Pharmacol.*, **106**, 739–745
- Jiang, C., Sarrel, P.M., Poole-Wilson, P.A., & Collins, P. (1992b) Acute effect of 17 $\beta$ -estradiol on rabbit coronary artery contractile responses to endothelin-1. *Am. J. Physiol.*, **263**, H271–H275
- Jiang, C., Sarrel, P.M., Lindsay, D.C., Poole-Wilson, P.A. & Collins, P. (1992c) Progesterone induces endothelium-independent relaxation of rabbit coronary artery *in vitro*. *Eur. J. Pharmacol.*, **211**, 163–167
- Jick, S.S., Walker, A.M. & Jick, H. (1993) Estrogens, progesterone, and endometrial cancer. *Epidemiology*, **4**, 20–24
- Johannisson, E., Holinka, C.F. & Arrenbrecht, S. (1997) Transdermal sequential and continuous hormone replacement regimens with estradiol and norethisterone acetate in postmenopausal women: Effects on the endometrium. *Int. J. Fertil. Womens Med.*, **42** (Suppl. 2), 388–398
- Jolleys, J.V. & Olesen, F. (1996) A comparative study of prescribing of hormone replacement therapy in USA and Europe. *Maturitas*, **23**, 47–53
- Jondet, M., Maroni, M., Yaneva, H., Brin, S., Peltier-Pujol, F. & Pelissier, C. (2002) Comparative endometrial histology in postmenopausal women with sequential hormone replacement

- therapy of estradiol and either chlormadinone acetate or micronized progesterone. *Maturitas*, **41**, 115–121
- Jordan, A. (2002) Toxicology of progestogens of implantable contraceptives for women. *Contraception*, **65**, 3–8
- Kanaya, A.M., Herrington, D., Vittinghoff, E., Lin, F., Grady, D., Bittner, V., Cauley, J.A. & Barrett-Connor, E. for the Heart and Estrogen/Progestin Replacement Study (2003) Glycemic effects of postmenopausal hormone therapy: The Heart and Estrogen/Progestin Replacement Study. A randomized, double-blind, placebo-controlled trial. *Ann. intern. Med.*, **138**, 1–9
- Karolinska Institutet (2007) [<http://www.imm.ki.se/CYPalleles/cyp1A1.htm>], accessed 20 December 2007
- Kawas, C., Resnick, S., Morrison, A., Brookmeyer, R., Corrada, M., Zonderman, A., Bacal, C., Lingle, D.D. & Metter, E. (1997) A prospective study of estrogen replacement therapy and the risk of developing Alzheimer's disease: The Baltimore Longitudinal Study of Aging. *Neurology*, **48**, 1517–1521
- Keam, S.J. & Wagstaff, A.J. (2003) Ethinylestradiol/drospirenone: A review of its use as an oral contraceptive. *Treat. Endocrinol.*, **2**, 49–70
- Kelley, K., Engqvist-Goldstein, A., Montali, J.A., Wheatley, J.B., Schmidt, D.E., Jr & Kauvar, L.M. (1994) Variability of glutathione S-transferase isoenzyme patterns in matched normal and cancer human breast tissue. *Biochem. J.*, **304**, 843–848
- Kennedy, D.L., Baum, C. & Forbes, M.B. (1985) Noncontraceptive estrogens and progestins: Use patterns over time. *Obstet. Gynecol.*, **65**, 441–446
- Kim-Schulze, S., McGowen, K.A., Hubchak, S.C., Cid, M.C., Martin, M.B., Kleinman, H.K., Greene, G.L. & Schnaper, H.W. (1996) Expression of an estrogen receptor by human coronary artery and umbilical vein endothelial cells. *Circulation*, **94**, 1402–1407
- King, C.D., Rios, G.R., Green, M.D. & Tephly, T.R. (2000) UDP-glucuronosyltransferases. *Curr. Drug Metab.*, **1**, 143–161
- Kirsh, V. & Kreiger, N. (2002) Estrogen and estrogen-progestin replacement therapy and risk of postmenopausal breast cancer in Canada. *Cancer Causes Control*, **13**, 583–590
- Kisselev, P., Schunck, W.-H., Roots, I. & Schwarz, D. (2005) Association of CYP1A1 polymorphisms with differential metabolic activation of 17 $\beta$ -estradiol and estrone. *Cancer Res.*, **65**, 2972–2978
- Klauber, N., Parangi, S., Flynn, E., Hamel, E. & D'Amato, R.J. (1997) Inhibition of angiogenesis and breast cancer in mice by the microtubule inhibitors 2-methoxyestradiol and taxol. *Cancer Res.*, **57**, 81–86
- Koh, K.K., Horne, M.K., III & Cannon, R.O., III (1999) Effects of hormone replacement therapy on coagulation, fibrinolysis, and thrombosis risk in postmenopausal women. *Thromb. Haemost.*, **82**, 626–633
- Kong, L.-Y., Szaniszló, P., Albrecht, T. & Liehr, J.G. (2000) Frequency and molecular analysis of *Hprt* mutations induced by estradiol in Chinese hamster V79 cells. *Int. J. Oncol.*, **17**, 1141–1149
- Krajcinovic, M., Ghadirian, P., Richer, C., Sinnett, H., Gandini, S., Perret, C., LaCroix, A., Labuda, D. & Sinnett, D. (2001) Genetic susceptibility to breast cancer in French-Canadians: Role of carcinogen-metabolizing enzymes and gene-environment interactions. *Int. J. Cancer*, **92**, 220–225
- Krattenmacher, R. (2000) Drospirenone: Pharmacology and pharmacokinetics of a unique progestogen. *Contraception*, **62**, 29–38

- Krebs, O., Schafer, B., Wolff, T., Oesterle, D., Deml, E., Sund, M. & Favor, J. (1998) The DNA damaging drug cyproterone acetate causes gene mutations and induces glutathione-S-transferase P in the liver of female Big Blue™ transgenic F344 rats. *Carcinogenesis*, **19**, 241–245
- Kronenberg, F., Cote, L.J., Linkie, D.M., Dyrenfurth, I. & Downey, J.A. (1984) Menopausal hot flashes: Thermoregulatory, cardiovascular, and circulating catecholamine and LH changes. *Maturitas*, **6**, 31–43
- Kumar, N., Koide, S.S., Tsong, Y.-Y. & Sundaram, K. (2000) Nestorone: A progestin with a unique pharmacological profile. *Steroids*, **65**, 629–636
- Kurman, R.J., Félix, J.C., Archer, D.F., Nanavati, N., Arce, J.-C. & Moyer, D.L. (2000) Norethindrone acetate and estradiol-induced endometrial hyperplasia. *Obstet. Gynecol.*, **96**, 373–379
- Lacey, J.V., Jr, Mink, P.J., Lubin, J.H., Sherman, M.E., Troisi, R., Hartge, P., Schatzkin, A. & Schairer, C. (2002) Menopausal hormone replacement therapy and risk of ovarian cancer. *J. Am. med. Assoc.*, **288**, 334–341
- Lachman, H.M., Papolos, D.F., Saito, T., Yu, Y.M., Szumlanski, C.L. & Weinshilboum, R.M. (1996) Human catechol-O-methyltransferase pharmacogenetics: Description of a functional polymorphism and its potential application to neuropsychiatric disorders. *Pharmacogenetics*, **6**, 243–250
- Larrea, F., Garcia-Beccera, R., Lemus, A.E., Garcia, G.A., Pérez-Palacios, Jackson, K.J., Coleman, K.M., Dace, R., Smith, C.L. & Cooney, A.J. (2001) A-ring reduced metabolites of 19-nor synthetic progestins as subtype selective agonists for ER $\alpha$ . *Endocrinology*, 3791–3799
- Larsen, M.C., Angus, W.G.R., Brake, P.B., Eltom, S.E., Sukow, K.A. & Jefcoate, C.R. (1998) Characterization of CYP1B1 and CYP1A1 expression in human mammary epithelial cells: Role of the aryl hydrocarbon receptor in polycyclic aromatic hydrocarbon metabolism. *Cancer Res.*, **58**, 2366–2374
- Lautala, P., Ulmanen, I. & Taskinen, J. (2001) Molecular mechanisms controlling the rate and specificity of catechol O-methylation by human soluble catechol O-methyltransferase. *Mol. Pharmacol.*, **59**, 393–402
- LaVallee, T.M., Zhan, X.H., Johnson, M.S., Herbstritt, C.J., Swartz, G., Williams, M.S., Hembrough, W.A., Green, S.J. & Pribluda, V.S. (2003) 2-Methoxyestradiol up-regulates death receptor 5 and induces apoptosis through activation of the extrinsic pathway. *Cancer Res.*, **63**, 468–475
- Lavigne, J.A., Goodman, J.E., Fonong, T., Odwin, S., He, P., Roberts, D.W. & Yager, J.D. (2001) The effects of catechol-O-methyltransferase inhibition on estrogen metabolite and oxidative DNA damage levels in estradiol-treated MCF-7 cells. *Cancer Res.*, **61**, 7488–7494
- Lee, A.J., Kosh, J.W., Conney, A.H. & Zhu, B.T. (2001) Characterization of the NADPH-dependent metabolism of 17 $\beta$ -estradiol to multiple metabolites by human liver microsomes and selectively expressed human cytochrome P450 3A4 and 3A5. *J. Pharmacol. exp. Ther.*, **298**, 420–432
- Lee, A.J., Mills, L.H., Kosh, J.W., Conney, A.H. & Zhu, B.T. (2002) NADPH-dependent metabolism of estrone by human liver microsomes. *J. Pharmacol. exp. Ther.*, **300**, 838–849
- Lee, A.J., Cai, M.X., Thomas, P.E., Conney, A.H. & Zhu, B.T. (2003a) Characterization of the oxidative metabolites of 17 $\beta$ -estradiol and estrone formed by 15 selectively expressed human cytochrome P450 isoforms. *Endocrinology*, **144**, 3382–3398

- Lee, A.J., Conney, A.H. & Zhu, B.T. (2003b) Human cytochrome P450 3A7 has a distinct high catalytic activity for the 16 $\alpha$ -hydroxylation of estrone but not 17 $\beta$ -estradiol. *Cancer Res.*, **63**, 6532–6536
- Lees, B. & Stevenson, J.C. (2001) The prevention of osteoporosis using sequential low-dose hormone replacement therapy with estradiol-17 $\beta$  and dydrogesterone. *Osteoporos. int.*, **12**, 251–258
- Lévesque, E., Beaulieu, M., Hum, D.W. & Bélanger, A. (1999) Characterization and substrate specificity of UGT2B4 (E<sup>458</sup>): A UDP-glucuronosyltransferase encoded by a polymorphic gene. *Pharmacogenetics*, **9**, 207–216
- Lewis, D.F.V., Gillam, E.M.J., Everett, S.A. & Shimada, T. (2003) Molecular modelling of human CYP1B1 substrate interactions and investigation of allelic variant effects on metabolism. *Chem.-biol. Interact.*, **145**, 281–295
- Li, C.I., Weiss, N.S., Stanford, J.L. & Daling, J.R. (2000) Hormone replacement therapy in relation to risk of lobular and ductal breast carcinoma in middle-aged women. *Cancer*, **88**, 2570–2577
- Li, D.N., Seidel, A., Pritchard, M.P., Wolf, C.R. & Friedberg, T. (2000) Polymorphisms in P450 *CYP1B1* affect the conversion of estradiol to the potentially carcinogenic metabolite 4-hydroxyestradiol. *Pharmacogenetics*, **10**, 343–353
- Li, J.J., Papa, D., Davis, M.F., Weroha, S.J., Aldaz, C.M., El Bayoumy, K., Ballenger, J., Tawfik, O. & Li, S.A. (2002) Ploidy differences between hormone- and chemical carcinogen-induced rat mammary neoplasms: Comparison to invasive human ductal breast cancer. *Mol. Carcinog.*, **33**, 56–65
- Li, C.I., Malone, K.E., Porter, P.L., Weiss, N.S., Tang, M.T., Cushing-Haugen, K.L. & Daling, J.R. (2003) Relationship between long durations and different regimens of hormone therapy and risk of breast cancer. *J. Am. med. Assoc.*, **289**, 3254–3263
- Li, K.-M., Todorovic, R., Devanesan, P., Higginbotham, S., Köfeler, H., Ramanathan, R., Gross, M.L., Rogen, E.G. & Cavalieri, E.L. (2004) Metabolism and DNA binding studies of 4-hydroxyestradiol and estradiol-3,4-quinone *in vitro* and in female ACI rat mammary gland *in vivo*. *Carcinogenesis*, **25**, 289–297
- Li, T., Sun, L., Miller, N., Nicklee, T., Woo, J., Hulse-Smith, L., Tsao, M.-S., Khokha, R., Martin, L. & Boyd, N. (2005) The association of measured breast tissue characteristics with mammographic density and other risk factors for breast cancer. *Cancer Epidemiol. Biomarkers Prev.*, **14**, 343–349
- Liang, Y.-L., Teede, H., Shiel, L.M., Thomas, A., Craven, R., Sachithanandan, N., McNeil, J.J., Cameron, J.D., Dart, A. & McGrath, B.P. (1997) Effects of oestrogen and progesterone on age-related changes in arteries of postmenopausal women. *Clin. exp. Pharmacol. Physiol.*, **24**, 457–459
- Liehr, J.G. & Ricci, M.J. (1996) 4-Hydroxylation of estrogens as marker of human mammary tumors. *Proc. natl Acad. Sci. USA*, **93**, 3294–3296
- Liehr, J.G., Fang, W.-F., Sirbasku, D.A. & Ari-Ulubelen, A. (1986) Carcinogenicity of catechol estrogens in Syrian hamsters. *J. steroid Biochem.*, **24**, 353–356
- de Lignières, B. (1999) Oral micronized progesterone. *Clin. Ther.*, **21**, 41–60
- Lin, A.L., McGill, H.C., Jr & Shain, S.A. (1982) Hormone receptors of the baboon cardiovascular system. Biochemical characterization of aortic and myocardial cytoplasmic progesterone receptors. *Circ. Res.*, **50**, 610–616
- Lin, P.-H., Nakamura, J., Yamaguchi, S., Asakura, S. & Swenberg, J.A. (2003) Aldehydic DNA lesions induced by catechol estrogens in calf thymus DNA. *Carcinogenesis*, **24**, 1133–1141

- Lindsay, R., Hart, D.M., Forrest, C. & Baird, C. (1980) Prevention of spinal osteoporosis in oophorectomised women. *Lancet*, **ii**, 1151–1154
- Lippert, C., Seeger, H., Wallwiener, D. & Mueck, A.O. (2000) Comparison of the effects of continuous combined and sequential combined medroxyprogesterone acetate–estradiol treatment on the proliferation of MCF-7 cells. *Climacteric*, **3**, 271–277
- Lippert, C., Seeger, H., Wallwiener, D. & Mueck, A.O. (2001) The effect of medroxyprogesterone acetate and norethisterone on the estradiol stimulated proliferation in MCF-7 cells: Comparison of continuous combined versus sequential combined estradiol/progestin treatment. *Eur. J. Gynaecol. Oncol.*, **22**, 331–335
- Lippert, C., Seeger, H., Wallwiener, D. & Mueck, A.O. (2002) Tibolone versus 17 $\beta$ -estradiol/norethisterone: Effects on the proliferation of human breast cancer cells. *Eur. J. Gynaec. Oncol.*, **23**, 127–130
- Lundberg, V., Tolonen, H., Stegmayr, B., Kuulasmaa, K. & Asplund, K. (2004) Use of oral contraceptives and hormone replacement therapy in the WHO MONICA project. *Maturitas*, **48**, 39–49
- Lundeen, S.G., Zhang, Z., Zhu, Y., Carver, J.M. & Winneker, R.C. (2001) Rat uterine complement C3 expression as a model for progesterone receptor modulators: Characterization of the new progestin trimegestone. *J. steroid Biochem. mol. Biol.*, **78**, 137–143
- Lundström, E., Wilczek, B., von Palffy, Z., Soderqvist, G. & von Schoultz, B. (2001) Mammographic breast density during hormone replacement therapy: Effects of continuous combination, unopposed transdermal and low-potency estrogen regimens. *Climacteric*, **4**, 42–48
- MacLaren, A. & Woods, N.F. (2001) Midlife women making hormone therapy decisions. *Womens Health Issues*, **11**, 216–230
- MacLennan, A.H., Taylor, A.W. & Wilson, D.H. (2004a) Hormone therapy use after the Women's Health Initiative. *Climacteric*, **7**, 138–142
- MacLennan, A.H., Broadbent, J.L., Lester, S. & Moore V. (2004b) Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. *The Cochrane Database Syst. Rev.*, **4**
- Magnusson, C., Baron, J.A., Correia, N., Bergstrom, R., Adami, H.O. & Persson, I. (1999) Breast-cancer risk following long-term oestrogen- and oestrogen-progestin-replacement therapy. *Int. J. Cancer*, **81**, 339–344
- Majumdar, S.R., Almasi, E.A. & Stafford, R.S. (2004) Promotion and prescribing of hormone therapy after report of harm by the Women's Health Initiative. *J. Am. med. Assoc.*, **292**, 1983–1988
- Malins, D.C. & Haimanot, R. (1991) Major alterations in the nucleotide structure of DNA in cancer of the female breast. *Cancer Res.*, **51**, 5430–5432
- Malins, D.C., Johnson, P.M., Wheeler, T.M., Barker, E.A., Polissar, N.L. & Vinson, M.A. (2001) Age-related radical-induced DNA damage is linked to prostate cancer. *Cancer Res.*, **61**, 6025–6028
- Mamdani, M.M., Tu, K., van Walraven, C., Austin, P.C. & Naylor, C.D. (2000) Postmenopausal estrogen replacement therapy and increased rates of cholecystectomy and appendectomy. *Can. med. Assoc. J.*, **162**, 1421–1424
- Manson, J.E., Hsia, J., Johnson, K.C., Rossouw, J.E., Assaf, A.R., Lasser, N.L., Trevisan, M., Black, H.R., Heckbert, S.R., Detrano, R., Strickland, O.L., Wong, N.D., Crouse, J.R., Stein, E. & Cushman, M. for the Women's Health Initiative Investigators (2003) Estrogen plus progestin and the risk of coronary heart disease. *New Engl. J. Med.*, **349**, 523–534

- Manzoli, L., Di Giovanni, P., Del Duca, L., De Aloysio, D., Festi, D., Capodicasa, S., Monastra, G., Romano, F. & Staniscia, T. (2004) Use of hormone replacement therapy in Italian women aged 50–70 years. *Maturitas*, **49**, 241–251
- Margolis, K.L., Bonds, D.F., Rodabough, R.J., Tinker, L., Phillips, L.S., Allen, C., Bassford, T., Burke, G., Torrens, J. & Howard, B.V. (2004) Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: Results from the Women's Health Initiative Hormone Trial. *Diabetologia*, **47**, 1175–1187
- Markushin, Y., Zhong, W., Cavalieri, E.L., Rogan, E.G., Small, G.J., Yeung, E.S. & Jankowiak, R. (2003) Spectral characterization of catechol estrogen quinone (CEQ)-derived DNA adducts and their identification in human breast tissue extract. *Chem. Res. Toxicol.*, **16**, 1107–1117
- Martelli, A., Mereto, E., Ghia, M., Orsi, P., Allavena, A., De Pascalis, C.R. & Brambilla, G. (1998) Induction of micronuclei and of enzyme-altered foci in the liver of female rats exposed to progesterone and three synthetic progestins. *Mutat. Res.*, **419**, 33–41
- Martelli, A., Mattioli, F., Carrozzino, R., Ferraris, E., Marchese, M., Angiola, M. & Brambilla, G. (1999) Genotoxicity testing of potassium canrenoate in cultured rat and human cells. *Mutagenesis*, **14**, 463–472
- Martelli, A., Carrozzino, R., Mattioli, F., Bucci, G., Lamarino, G. & Brambilla, G. (2002) DNA damage in tissues of rat treated with potassium canrenoate. *Toxicology*, **171**, 95–103
- Martelli, A., Mattioli, F., Angiola, M., Reimann, R. & Brambilla, G. (2003) Species, sex and inter-individual differences in DNA repair induced by nine sex steroids in primary cultures of rat and human hepatocytes. *Mutat. Res.*, **536**, 69–78
- Mattioli, F., Garbero, C., Gosmar, M., Manfredi, V., Carrozzino, R., Martelli, A. & Brambilla, G. (2004) DNA fragmentation, DNA repair and apoptosis induced in primary rat hepatocytes by dienogest, dydrogesterone and 1,4,6-androstatriene-17 $\beta$ -ol-3-one acetate. *Mutat. Res.*, **564**, 21–29
- Maugard, C.M., Charrier, J., Pitard, A., Campion, L., Akande, O., Pleasants, L. & Ali-Osman, F. (2001) Genetic polymorphism at the glutathione S-transferase (GST) P1 locus is a breast cancer risk modifier. *Int. J. Cancer*, **91**, 334–339
- McFadyen, M.C.E., Breeman, S., Payne, S., Stirk, C., Miller, I.D., Melvin, W.T. & Murray, G.I. (1999) Immunohistochemical localization of cytochrome P450 CYP1B1 in breast cancer with monoclonal antibodies specific for CYP1B1. *J. Histochem. Cytochem.*, **47**, 1457–1464
- McGrath, M., Hankinson, S.E., Arbeitman, L., Colditz, G.A., Hunter, D.J. & De Vivo, I. (2004) Cytochrome P450 1B1 and catechol-O-methyltransferase polymorphisms and endometrial cancer susceptibility. *Carcinogenesis*, **25**, 559–565
- McKnight, B., Voigt, L.F., Beresford, S.A. & Weiss, N.S. (1998) Re: Estrogen-progestin replacement therapy and endometrial cancer. *J. natl Cancer Inst.*, **90**, 164–166
- McLellan, R.A., Oscarson, M., Hidestrand, M., Leidvik, B., Jonsson, E., Otter, C. & Ingelman-Sundberg, M. (2000) Characterization and functional analysis of two common human cytochrome P450 1B1 variants. *Arch. Biochem. Biophys.*, **378**, 175–181
- Meilahn, E.N., De Stavola, B., Allen, D.S., Fentiman, I., Bradlow, H.L., Sepkovic, D.W. & Kuller, L.H. (1998) Do urinary oestrogen metabolites predict breast cancer? Guernsey III cohort follow-up. *Br. J. Cancer*, **78**, 1250–1255
- Mendoza, N., Pisón, J.A., Fernandez, M., Sánchez, M.C., Malde, J. & Miranda, J.A. (2002) Prospective, randomised study with three HRT regimens in postmenopausal women with an intact uterus. *Maturitas*, **41**, 289–298

- Mercuro, G., Pitzalis, L., Podda, A., Zoncu, S., Pilia, I., Melis, G.B. & Cherchi, A. (1999) Effects of acute administration of natural progesterone on peripheral vascular responsiveness in healthy postmenopausal women. *Am. J. Cardiol.*, **84**, 214–218
- Merom, D., Ifrah, A., Cohen-Manheim, I., Chinich, A. & Green, M.S. (2002) Factors predicting current use of hormone replacement therapy among menopausal Jewish women in Israel. The National Women's Health Interview Survey, 1998. *Israeli med. Assoc. J.*, **4**, 671–676
- Metcalfe, S. (2004) *HT Use in New Zealand: A Patient-level Analysis of Pharmhouse Data*, unpublished report released under the Official Information Act, October 2004
- Michnovicz, J.J., Hershcopf, R.J., Naganuma, H., Bradlow, H.L. & Fishman, J. (1986) Increased 2-hydroxylation of estradiol as a possible mechanism for the anti-estrogenic effect of cigarette smoking. *New Engl. J. Med.*, **315**, 1305–1309
- Miettinen, M., Mustonen, M., Poutanen, M., Isomaa, V., Wickman, M., Soderqvist, G., Vihko, R. & Vihko, P. (1999) 17 $\beta$ -Hydroxysteroid dehydrogenases in normal human mammary epithelial cells and breast tissue. *Breast Cancer Res. Treat.*, **57**, 175–182
- Mikkola, T.S. & Clarkson, T.B. (2002) Estrogen replacement therapy, atherosclerosis, and vascular function. *Cardiovasc. Res.*, **53**, 605–619
- Mikkola, T., Viinikka, L. & Ylikorkala, O. (1998) Estrogen and postmenopausal estrogen/progestin therapy: Effect on endothelium-dependent prostacyclin, nitric oxide and endothelin-1 production. *Eur. J. Obstet. Gynecol.*, **79**, 75–82
- Milewicz, T., Gregoraszcuk, E.L., Sztefko, K., Augustowska, K., Krzysiek, J. & Rys, J. (2005a) Lack of synergy between estrogen and progesterone on local IGF-I, IGFBP-3 and IGFBP-2 secretion by both hormone-dependent and hormone-independent breast cancer explants in vitro. Effect of tamoxifen and mifepristone (RU 486). *Growth Horm. IGF Res.*, **15**, 140–147
- Milewicz, T., Gregoraszcuk, E.L., Augustowska, K., Krzysiek, J., Sztefko, K. & Rys, J. (2005b) Progesterone but not estradiol-17 $\beta$  potentiates local GH secretions by hormone-dependent breast cancer explants. An *in vitro* study. *Exp. clin. Endocrinol. Diabetes*, **113**, 127–132
- Miller, V.M. & Vanhoutte, P.M. (1991) Progesterone and modulation of endothelium-dependent responses in canine coronary arteries. *Am. J. Physiol.*, **261**, R1022–R1027
- Million Women Study Collaborators (2002) Patterns of use of hormone replacement therapy in one million women in Britain, 1996–2000. *Br. J. Obstet. Gynaecol.*, **109**, 1319–1330
- Million Women Study Collaborators (2005) Endometrial cancer and hormone-replacement therapy in the Million Women Study. *Lancet*, **365**, 1543–1551
- Mills, L.H., Lee, A.J., Parlow, A.F. & Zhu, B.T. (2001) Preferential growth stimulation of mammary glands over uterine endometrium in female rats by a naturally occurring estradiol-17 $\beta$ -fatty acid ester. *Cancer Res.*, **61**, 5764–5770
- Miners, J.O., McKinnon, R.A. & Mackenzie, P.I. (2002) Genetic polymorphisms of UDP-glucuronosyltransferases and their functional significance. *Toxicology*, **181–182**, 453–456
- Mitrunen, K. & Hirvonen, A. (2003) Molecular epidemiology of sporadic breast cancer. The role of polymorphic genes involved in oestrogen biosynthesis and metabolism. *Mutat. Res.*, **544**, 9–41
- Miyairi, S., Maeda, K., Oe, T., Kato, T. & Naganuma, A. (1999) Effect of metal ions on the stable adduct formation of 16 $\alpha$ -hydroxyestrone with a primary amine via the Heyns rearrangement. *Steroids*, **64**, 252–258

- Miyoshi, Y., Ando, A., Shiba, E., Taguchi, T., Tamaki, Y. & Noguchi, S. (2001) Involvement of up-regulation of 17 $\beta$ -hydroxysteroid dehydrogenase type 1 in maintenance of intratumoral high estradiol levels in postmenopausal breast cancers. *Int. J. Cancer*, **94**, 685–689
- Mizunuma, H., Honjo, H., Aso, T., Urabe, M., Ohta, H., Kobayashi, S., Sagara, Y., Sanada, M., Tanaka, K., Dobashi, K., Hayashi, K. & Ohama, K. (2001) Postmenopausal hormone replacement therapy use and risk of endometrial cancer in Japanese women. *Climacteric*, **4**, 293–298
- Mrusek, S., Classen-Linke, I., Vloet, A., Beier, H.M. & Krusche, C.A. (2005) Estradiol and medroxyprogesterone acetate regulated genes in T47D breast cancer cells. *Mol. cell. Endocrinol.*, **235**, 39–50
- Mueck, A.O., Seeger, H., Gräser, T., Oettel, M. & Lippert, T.H. (2001) The effects of postmenopausal hormone replacement therapy and oral contraceptives on the endogenous estradiol metabolism. *Horm. Metab. Res.*, **33**, 744–747
- Mueck, A.O., Seeger, H. & Wallwiener, D. (2002) Impact of hormone replacement therapy on endogenous estradiol metabolism in postmenopausal women. *Maturitas*, **43**, 87–93
- Mueck, A.O., Seeger, H. & Wallwiener, D. (2003) Comparison of the proliferative effects of estradiol and conjugated equine estrogens on human breast cancer cells and impact of continuous combined progestogen addition. *Climacteric*, **6**, 221–227
- Mueller, J.E., Döring, A., Heier, M. & Löwel, H. (2002) Prevalence and determinants of hormone replacement therapy in German women 1984–1995. *Maturitas*, **43**, 95–104
- Mulnard, R.A., Cotman, C.W., Kawas, C., van Dyck, C.H., Sano, M., Doody, R., Koss, E., Pfeiffer, E., Jin, S., Gamst, A., Grundman, M., Thomas, R. & Thal, L.J. for the Alzheimer's Disease Cooperative Study (2000) Estrogen replacement therapy for treatment of mild to moderate Alzheimer disease. A randomized controlled trial. *J. Am. med. Assoc.*, **283**, 1007–1015
- Murray, G.I., Taylor, M.C., McFadyen, M.C.E., McKay, J.A., Greenlee, W.F., Burke, M.D. & Melvin, W.T. (1997) Tumor-specific expression of cytochrome P450 CYP1B1. *Cancer Res.*, **57**, 3026–3031
- Murray, G.I., Melvin, W.T., Greenlee, W.F. & Burke, M.D. (2001) Regulation, function, and tissue-specific expression of cytochrome P450 CYP1B1. *Ann. Rev. Pharmacol. Toxicol.*, **41**, 297–316
- Musarrat, J., Arezina-Wilson, J. & Wani, A.A. (1996) Prognostic and aetiological relevance of 8-hydroxyguanosine in human breast carcinogenesis. *Eur. J. Cancer*, **32A**, 1209–1214
- Muti, P., Bradlow, H.L., Micheli, A., Krogh, V., Freudenheim, J.L., Schünemann, H.J., Stanulla, M., Yang, J., Sepkovic, D.W., Trevisan, M. & Berrino, F. (2000) Estrogen metabolism and risk of breast cancer: A prospective study of the 2:16 $\alpha$ -hydroxyestrone ratio in premenopausal and postmenopausal women. *Epidemiology*, **11**, 635–640
- Nachtigall, L.E., Nachtigall, R.H., Nachtigall, R.D. & Beckman, E.M. (1979) Estrogen replacement therapy. I: A 10 year prospective study in the relationship to osteoporosis. *Obstet. Gynecol.*, **53**, 277–281
- Nakamura, M., Katsuki, Y., Shibutani, Y. & Oikawa, T. (1999) Dienogest, a synthetic steroid, suppresses both embryonic and tumor-cell-induced angiogenesis. *Eur. J. Pharmacol.*, **386**, 33–40
- Negri, E., Tzonou, A., Beral, V., Laggiou, P., Trichopoulos, D., Parazzini, F., Franceschi, S., Booth, M. & La Vecchia, C. (1999) Hormonal therapy for menopause and ovarian cancer in a collaborative re-analysis of European studies. *Int. J. Cancer*, **80**, 848–851



- Nelson, H.D., Humphrey, L.L., LeBlanc, E., Miller, J., Takano, L., Chan, B.K.S., Nygren, P., Allan, J.D. & Teutsch, S.M. (2002a) *Postmenopausal Hormone Replacement Therapy for the Primary Prevention of Chronic Conditions: A Summary of the Evidence for the U.S. Preventive Services Task Force*. [https://www.preventiveservices.ahrq.gov]
- Nelson, H.D., Humphrey, L.L., Nygren, P., Teutsch, S.M. & Allan, J.D. (2002b) Postmenopausal hormone replacement therapy. *J. Am. med. Assoc.*, **288**, 872–881
- Neven, P., Quail, D., Levrier, M., Aguas, F., Thé, H.S., De Geyter, C., Glant, M.D., Beck, H., Bosio-LeGoux, B., Schmitt, H., Hottgenroth, A. & Nickelsen, T. (2004) Uterine effects of estrogen plus progestin therapy and raloxifene: Adjudicated results from the EURALOX study. *Obstet. Gynecol.*, **103**, 881–891
- Newbold, R.R. & Liehr, J.G. (2000) Induction of uterine adenocarcinoma in CD-1 mice by catechol estrogens. *Cancer Res.*, **60**, 235–237
- Newcomb, P.A. & Storer, B.E. (1995) Postmenopausal hormone use and risk of large-bowel cancer. *J. natl Cancer Inst.*, **87**, 1067–71
- Newcomb, P.A. & Trentham-Dietz, A. (2003) Patterns of postmenopausal progestin use with estrogen in relation to endometrial cancer (United States). *Cancer Causes Control*, **14**, 195–201
- Newcomb, P.A., Titus-Ernstoff, L., Egan, K.M., Trentham-Dietz, A., Baron, J.A., Storer, B.E., Willett, W.C. & Stampfer, M.J. (2002) Postmenopausal estrogen and progestin use in relation to breast cancer risk. *Cancer Epidemiol. Biomarkers Prev.*, **11**, 593–600
- Nichols, H.B., Trentham-Dietz, A., Hampton, J.M. & Newcomb, P.A. (2005) Oral contraceptives use, reproductive factors, and colorectal cancer risk: Findings from Wisconsin. *Cancer Epidemiol. Biomarkers Prev.*, **14**, 1212–1218
- Normand, T., Narod, S., Labrie, F. & Simard, J. (1993) Detection of polymorphisms in the estradiol 17 $\alpha$ -hydroxysteroid dehydrogenase II gene at the EDH17B2 locus on 17q11-q21. *Hum. mol. Genet.*, **2**, 479–483
- North American Menopause Society (2004) Recommendations for estrogen and progestogen use in peri- and postmenopausal women: October 2004 position statement of The North American Menopause Society. *Menopause*, **11**, 589–600
- Nugent, A.G., Leung, K.-C., Sullivan, D., Reutens, A.T. & Ho, K.K.Y. (2003) Modulation by progestogens of the effects of oestrogen on hepatic endocrine function in postmenopausal women. *Clin. Endocrinol.*, **59**, 690–698
- Oduwole, O.O., Li, Y., Isomaa, V.V., Mäntyniemi, A., Pulkka, A.E., Soini, Y. & Vihko, P.T. (2004) 17 $\beta$ -Hydroxysteroid dehydrogenase type 1 is an independent prognostic marker in breast cancer. *Cancer Res.*, **64**, 7604–7609
- Oehler, M.K., MacKenzie, I.Z., Wallwiener, D., Bicknell, R. & Rees, M.C.P. (2002) Wnt-7a is up-regulated by norethisterone in human endometrial epithelial cells: A possible mechanism by which progestogens reduce the risk of estrogen-induced endometrial neoplasia. *Cancer Lett.*, **186**, 75–81
- Olsson, H.L., Ingvar, C. & Bladstrom, A. (2003) Hormone replacement therapy containing progestins and given continuously increases breast carcinoma risk in Sweden. *Cancer*, **97**, 1387–1392
- Ory, K., Lebeau, J., Levalois, C., Bishay, K., Fouchet, P., Allemand, I., Therwath, A. & Chevillard, S. (2001) Apoptosis inhibition mediated by medroxyprogesterone acetate treatment of breast cancer cell lines. *Breast Cancer Res. Treat.*, **68**, 187–198
- Paganini-Hill, A. (1999) Estrogen replacement therapy and colorectal cancer risk in elderly women. *Dis. Colon Rectum*, **42**, 1300–1305

- Paganini-Hill, A. & Henderson, V.W. (1994) Estrogen deficiency and risk of Alzheimer's disease in women. *Am. J. Epidemiol.*, **140**, 256–261
- Pahuja, S.L., Zielinski, J.E., Giordano, G., McMurray, W.J. & Hochberg, R.B. (1991) The biosynthesis of D-ring fatty acid esters of estriol. *J. biol. Chem.*, **266**, 7410–7416
- Palmund, I. (1997) The social construction of menopause as risk. *J. psychosom. Obstet. Gynaecol.*, **18**, 87–94
- Paria, B.C., Lim, H., Wang, X.-N., Liehr, J., Das, S.K. & Dey, S.K. (1998) Coordination of differential effects of primary estrogen and catecholesterogen on two distinct targets mediates embryo implantation in the mouse. *Endocrinology*, **139**, 5235–5246
- Paria, B.C., Lim, H., Das, S.K., Reese, J. & Dey, S.K. (2000) Molecular signaling in uterine receptivity for implantation. *Semin. Cell dev. Biol.*, **11**, 67–76
- Pasapera, A.M., Gutierrez-Sagal, R., Herrera, J., Galicia-Canales, N., Garcia de la More, M. & Ulloa-Aguirre, A. (2002) Norethisterone is bioconverted to oestrogenic compounds that activate both the oestrogen receptor  $\alpha$  and oestrogen receptor  $\beta$  in vitro. *Eur. J. Pharmacol.*, **452**, 347–355
- Pasley, B.H., Standfast, S.J. & Katz, S.H. (1984) Prescribing estrogen during menopause: Physician survey of practices in 1974 and 1981. *Public Health Rep.*, **99**, 424–429
- Pasqualini, J.R. (2003) Differential effects of progestins on breast tissue enzymes. *Maturitas*, **46** (Suppl. 1), S45–S54
- Pasqualini, J.R. (2004) The selective estrogen enzyme modulators in breast cancer: A review. *Biochim. biophys. Acta*, **1654**, 123–143
- Pasqualini, J.R. & Chetrite, G. (2001) Paradoxical effect of estradiol: It can block its own bioformation in human breast cancer cells. *J. steroid Biochem. mol. Biol.*, **78**, 21–24
- Pasqualini, J.R., Chetrite, G., Blacker, C., Feinstein, M.-C., Delalonde, L., Talbi, M. & Maloche, C. (1996) Concentrations of estrone, estradiol, and estrone sulfate and evaluation of sulfatase and aromatase activities in pre- and postmenopausal breast cancer patients. *J. clin. Endocrinol. Metab.*, **81**, 1460–1464
- Pecci, A., Scholz, A., Pelster, D. & Beato, M. (1997) Progestins prevent apoptosis in a rat endometrial cell line and increase the ratio of *bcl-X<sub>L</sub>* to *bcl-X<sub>s</sub>*. *J. biol. Chem.* **272**, 11791–11798
- Pedersen, L.C., Petrotchenko, E., Shevtsov, S. & Negishi, M. (2002) Crystal structure of the human estrogen sulfotransferase-PAPS complex: Evidence for catalytic role of Ser<sup>137</sup> in the sulfuryl transfer reaction. *J. biol. Chem.*, **277**, 17928–17932
- Peltoketo, H., Isomaa, V., Poutanen, M. & Vihko, R. (1996) Expression and regulation of 17 $\beta$ -hydroxysteroid dehydrogenase type 1. *J. Endocrinol.*, **150** (Suppl.), 21–30
- Peltoketo, H., Vihko, P. & Vihko, R. (1999) Regulation of estrogen action: Role of 17 $\beta$ -hydroxysteroid dehydrogenases. *Vitam. Horm.*, **55**, 353–398
- Penning, T.M., Burczynski, M.E., Jez, J.M., Hung, C.-F., Lin, H.-K., Ma, H., Moore, M., Palackal, N. & Ratnam, K. (2000) Human 3 $\alpha$ -hydroxysteroid dehydrogenase isoforms (AKR1C1-AKR1C4) of the aldo-keto reductase superfamily: Functional plasticity and tissue distribution reveals roles in the inactivation and formation of male and female sex hormones. *Biochem. J.*, **351**, 67–77
- Penotti, M., Nencioni, T., Gabrielli, L., Farina, M., Castiglioni, E. & Polvani, F. (1993) Blood flow variations in internal carotid and middle cerebral arteries induced by postmenopausal hormone replacement therapy. *Am. J. Obstet. Gynecol.*, **169**, 1226–1232

- Persson, I., Adami, H.-O., Bergkvist, L., Lindgren, A., Pettersson, B., Hoover, R. & Schairer, C. (1989) Risk of endometrial cancer after treatment with oestrogens alone or in conjunction with progestogens: Results of a prospective study. *Br. med. J.*, **298**, 147–151
- Persson, I., Yuen, J., Bergkvist, L. & Schairer, C. (1996) Cancer incidence and mortality in women receiving estrogen and estrogen-progestin replacement therapy — Long-term follow-up of a Swedish cohort. *Int. J. Cancer*, **67**, 327–332
- Persson, I., Weiderpass, E., Bergkvist, L., Bergstrom, R. & Schairer, C. (1999) Risks of breast and endometrial cancer after estrogen and estrogen-progestin replacement. *Cancer Causes Control*, **10**, 253–260
- Petitti, D.B. (1994) Coronary heart disease and estrogen replacement therapy. Can compliance bias explain the results of observational studies? *Ann. Epidemiol.*, **4**, 115–118
- Peverill, R.E. (2003) Hormone therapy and venous thromboembolism. *Best Pract. and Res. clin. Endocrin. Metab.*, **17**, 149–164
- Pike, M.C., Peters, R.K., Cozen, W., Probst-Hensch, N.M., Felix, J.C., Wan, P.C. & Mack, T.M. (1997) Estrogen-progestin replacement therapy and endometrial cancer. *J. natl Cancer Inst.*, **89**, 1110–1116
- Pike, M.C., Pearce, C.L., Peters, R., Cozen, W., Wan, P. & Wu, A.H. (2004) Hormonal factors and the risk of invasive ovarian cancer: A population-based case-control study. *Fertil. Steril.*, **82**, 186–195
- Pollow, K., Juchem, M., Elger, W., Jacobi, N., Hoffmann, G. & Mobus, V. (1992) Dihydrospirorenone (ZK30595): A novel synthetic progestagen — Characterization of binding to different receptor proteins. *Contraception*, **46**, 561–574
- Portman, D.J., Symons, J.P., Wilborn, W. & Kempfert, N.J. (2003) A randomized, double-blind, placebo-controlled, multicenter study that assessed the endometrial effects of norethindrone acetate plus ethinyl estradiol versus ethinyl estradiol alone. *Am. J. Obstet. Gynecol.*, **188**, 334–342
- Post, W.S., Goldschmidt-Clermont, P.J., Wilhide, C.C., Heldman, A.W., Sussman, M.S., Ouyang, P., Milliken, E.E. & Issa, J.P. (1999) Methylation of the estrogen receptor gene is associated with aging and atherosclerosis in the cardiovascular system. *Cardiovasc. Res.*, **43**, 985–991
- Post, M.S., Christella, M., Thomassen, L.G.D., van der Mooren, M.J., van Baal, W.M., Rosing, J., Kenemans, P. & Stehouwer, C.D.A. (2003) Effect of oral and transdermal estrogen replacement therapy on hemostatic variables associated with venous thrombosis. A randomized, placebo-controlled study in postmenopausal women. *Arterioscler. Thromb. vasc. Biol.*, **23**, 1116–1121
- Poutanen, M., Isomaa, V., Kainulainen, K. & Vihko, R. (1990) Progestin induction of 17 $\beta$ -hydroxysteroid dehydrogenase enzyme protein in the T-47D human breast-cancer cell line. *Int. J. Cancer*, **46**, 897–901
- Poutanen, M., Isomaa, V., Lehto, V.-P. & Vihko, R. (1992a) Immunological analysis of 17 $\beta$ -hydroxysteroid dehydrogenase in benign and malignant human breast tissue. *Int. J. Cancer*, **50**, 386–390
- Poutanen, M., Moncharmont, B. & Vihko, R. (1992b) 17 $\beta$ -Hydroxysteroid dehydrogenase gene expression in human breast cancer cells: Regulation of expression by a progestin. *Cancer Res.*, **52**, 290–294
- Pradhan, A.D., Manson, J.E., Rossouw, J.E., Siscovick, D.S., Mouton, C.P., Rifai, N., Wallace, R.B., Jackson, R.D., Pettinger, M.B. & Ridker, P.M. (2002) Inflammatory biomarkers,

- hormone replacement therapy, and incident coronary heart disease: Prospective analysis from the Women's Health Initiative Observational Study. *J. Am. med. Assoc.*, **288**, 980–987
- Prentice, R.L., Langer, R., Stefanick, M.L., Howard, B.V., Pettinger, M., Anderson, G., Barad, D., Curb, J.D., Kotchen, J., Kuller, L., Limacher, M. & Wactawski-Wende, J. for the Women's Health Initiative Investigators. (2005) Combined postmenopausal hormone therapy and cardiovascular disease: Toward resolving the discrepancy between observational studies and the Women's Health Initiative Clinical Trial. *Am. J. Epidemiol.*, **162**, 404–414
- Preston, R.A., White, W.B., Pitt, B., Bakris, G., Norris, P.M. & Hanes, V. (2005) Effects of drospirenone/17 $\beta$ -estradiol on blood pressure and potassium balance in hypertensive postmenopausal women. *Am. J. Hypertens.*, **18**, 797–804
- Pribluda, V.S., Gubish, E.R., Jr, LaVallee, T.M., Treston, A., Swartz, G.M. & Green, S.J. (2000) 2-Methoxyestradiol: An endogenous antiangiogenic and antiproliferative drug candidate. *Cancer Metast. Rev.*, **19**, 173–179
- Prihartono, N., Palmer, J.R., Louik, C., Shapiro, S. & Rosenberg, L. (2000) A case-control study of use of postmenopausal female hormone supplements in relation to the risk of large bowel cancer. *Cancer Epidemiol. Biomarkers Prev.*, **9**, 443–447
- Progetto Menopausa Italia Study Group (2001) General and medical factors associated with hormone replacement therapy among women attending menopause clinics in Italy. *Menopause*, **8**, 290–295
- Pukkala, E., Tulenheimo-Silfvast, A. & Leminen, A. (2001) Incidence of cancer among women using long versus monthly cycle hormonal replacement therapy, Finland 1994–1997. *Cancer Causes Control*, **12**, 111–115
- Puranen, T.J., Poutanen, M.H., Peltoketo, H.E., Vihko, P.T. & Vihko, R.K. (1994) Site-directed mutagenesis of the putative active site of human 17 $\beta$ -hydroxysteroid dehydrogenase type 1. *Biochem. J.*, **304**, 289–293
- Purdie, D.M., Bain, C.J., Siskind, V., Russell, P., Hacker, N.F., Ward, B.G., Quinn, M.A. & Green, A.C. (1999) Hormone replacement therapy and risk of epithelial ovarian cancer. *Br. J. Cancer*, **81**, 559–563
- Raafat, A.M., Hofseth, L.J., Li, S., Bennett, J.M. & Haslam, S.Z. (1999) A mouse model to study the effects of hormone replacement therapy on normal mammary gland during menopause: Enhanced proliferative response to estrogen in late postmenopausal mice. *Endocrinology*, **140**, 2570–2580
- Raafat, A.M., Hofseth, L.J. & Haslam, S.Z. (2001) Proliferative effects of combination estrogen and progesterone replacement therapy on the normal postmenopausal mammary gland in a murine model. *Am. J. Obstet. Gynecol.*, **184**, 340–349
- Rabe, T., Bohlmann, M.K., Rehberger-Schneider, S. & Prifti, S. (2000) Induction of estrogen receptor- $\alpha$  and - $\beta$  activities by synthetic progestins. *Gynecol. Endocrinol.*, **14**, 118–126
- Rachon, D., Zdrojewski, T., Suchecka-Rachon, K., Szpakowski, P., Bandosz, P., Manikowski, A. & Wyrzykowski, B. (2004) Knowledge and use of hormone replacement therapy among Polish women: Estimates from a nationally representative study HORTPOL 2002. *Maturitas*, **47**, 31–37
- Raftogianis, R., Creveling, C., Weinshilboum, R. & Weisz, J. (2000) Estrogen metabolism by conjugation. *J. natl Cancer Inst. Monogr.*, **27**, 113–124

- Rajakpaxe, N., Butterworth, M. & Kortenkamp, A. (2005) Detection of DNA strand breaks and oxidized DNA bases at the single-cell level resulting from exposure to estradiol and hydroxylated metabolites. *Environ. mol. Mutag.*, **45**, 397–404
- Ramanathan, R., Cao, K., Cavalieri, E. & Gross, M.L. (1998) Mass spectrometric methods for distinguishing structural isomers of glutathione conjugates of estrone and estradiol. *J. Am. Soc. mass Spectrom.*, **9**, 612–619
- Rapp, S.R., Espeland, M.A., Shumaker, S.A., Henderson, V.W., Brunner, R.L., Manson, J.E., Gass, M.L.S., Stefanick, M.L., Lane, D.S., Hays, J., Johnson, K.C., Coker, L.H., Dailey, M. & Bowen, D. for the WHIMS Investigators (2003) Effect of estrogen plus progestin on global cognitive function in postmenopausal women: The Women's Health Initiative Memory Study: A randomized controlled trial. *J. Am. med. Assoc.*, **289**, 2663–2672
- Raudaskoski, T., Knip, M. & Laatikainen, T. (1998) Plasma insulin-like growth factor-I and its binding proteins 1 and 3 during continuous nonoral and oral combined hormone replacement therapy. *Menopause*, **5**, 217–222
- Reboussin, B.A., Greendale, G.A. & Espeland, M.A. (1998) Effect of hormone replacement therapy on self-reported cognitive symptoms: Results from the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *Climacteric*, **1**, 172–179
- Recker, R.R., Davies, M., Dowd, R.M. & Heaney, R.P. (1999) The effect of low-dose continuous estrogen and progesterone therapy with calcium and vitamin D on bone in elderly women. A randomized, controlled trial. *Ann. intern. Med.*, **130**, 897–904
- Reis, S.E., Gloth, S.T., Blumenthal, R.S., Resar, J.R., Zacur, H.A., Gerstenblith, G. & Brinker, J.A. (1994) Ethinyl estradiol acutely attenuates abnormal coronary vasomotor responses to acetylcholine in postmenopausal women. *Circulation*, **89**, 52–60
- Ridker, P.M., Hennekens, C.H., Rifai, N., Buring, J.E. & Manson, J.E. (1999) Hormone replacement therapy and increased plasma concentration of C-reactive protein. *Circulation*, **100**, 713–716
- Ridker, P.M., Hennekens, C.H., Buring, J.E. & Rifai, N. (2000) C-Reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *New Engl. J. Med.*, **342**, 836–843
- Rijpkema, A.H.M., van der Sanden, A.A. & Ruijs, A.H.C. (1990) Effects of post-menopausal oestrogen–progestogen replacement therapy on serum lipids and lipoproteins: A review. *Maturitas*, **12**, 259–285
- Riman, T., Dickman, P.W., Nilsson, S., Correia, N., Nordlinder, H., Magnusson, C.M. & Persson, I.R. (2001) Risk factors for epithelial borderline ovarian tumors: Results of a Swedish case-control study. *Gynecol. Oncol.*, **83**, 575–585
- Riman, T., Dickman, P.W., Nilsson, S., Correia, N., Nordlinder, H., Magnusson, C.M., Weiderpass, E. & Persson, I.R. (2002) Hormone replacement therapy and the risk of invasive epithelial ovarian cancer in Swedish women. *J. natl Cancer Inst.*, **94**, 497–504
- Risch, H.A. & Howe, G.R. (1995) Menopausal hormone use and colorectal cancer in Saskatchewan: A record linkage cohort study. *Cancer Epidemiol. Biomarkers Prev.*, **4**, 21–28
- Rodriguez, C., Calle, E.E., Patel, A.V., Tatham, L.M., Jacobs, E.J. & Thun, M.J. (2001) Effect of body mass on the association between estrogen replacement therapy and mortality among elderly US women. *Am. J. Epidemiol.*, **153**, 145–152
- Rogan, E.G., Badawi, A.F., Devanesan, P.D., Meza, J.L., Edney, J.A., West, W.W., Higginbotham, S.M. & Cavalieri, E.L. (2003) Relative imbalances in estrogen metabolism and conjugation in

- breast tissue of women with carcinoma: Potential biomarkers of susceptibility to cancer. *Carcinogenesis*, **24**, 697–702
- Rosano, G.M.C., Mercurio, G., Vitale, C., Rossini, P., Galetta, P. & Fini, M. (2001) How progestins influence the cardiovascular effect of hormone replacement therapy. *Gynecol. Endocrinol.*, **15** (Suppl. 6), 9–17
- Rosano, G.M.C., Vitale, C., Silvestri, A. & Fini, M. (2003) Metabolic and vascular effect of progestins in post-menopausal women. Implications for cardioprotection. *Maturitas*, **46** (Suppl. 1), S17–S29
- Rosano, G.M.C., Vitale, C. & Lello, S. (2004) Postmenopausal hormone therapy: Lessons from observational and randomized studies. *Endocrine*, **24**, 251–254
- Rosano, G.M.C., Collins, P., Gerbara, O., Sheiban, I., Silvestri, A., Wajngarten, M., Ramires, J.A., Fini, M. & Mercurio, G. (2006) Effect of estradiol 17 $\beta$  upon coronary artery vasoconstrictor response to methylergometrine maleate in female menopausal patients. *Int. J. Cardiol.*, **107**, 254–259
- Ross, R.K., Paganini-Hill, A., Mack, T.M., Arthur, M. & Henderson, B.E. (1981) Menopausal oestrogen therapy and protection from death from ischaemic heart disease. *Lancet*, **i**, 858–860
- Ross, D., Godfree, V., Cooper, A., Pryse-Davies, J. & Whitehead, M.I. (1997) Endometrial effects of three doses of trimegestone, a new orally active progestogen, on the postmenopausal endometrium. *Maturitas*, **28**, 83–88
- Ross, R.K., Paganini-Hill, A., Wan, P.C. & Pike, M.C. (2000) Effect of hormone replacement therapy on breast cancer risk: Estrogen versus estrogen plus progestin. *J. natl Cancer Inst.*, **92**, 328–332
- Rossouw, J.E. (2000) Debate: The potential role of estrogen in the prevention of heart disease in women after menopause. *Curr. Control Trials cardiovasc. Med.*, **1**, 135–138
- Rossouw, J.E., Anderson, G.L., Prentice, R.L., LaCroix, A.Z., Kooperberg, C., Stefanick, M.L., Jackson, R.D., Beresford, S.A.A., Howard, B.V., Johnson, K.C., Kotchen, J.M. & Ockene, J. for the Writing Group for the Women's Health Initiative Investigators (2002) Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative Randomized Controlled Trial. *J. Am. med. Assoc.*, **288**, 321–333
- Roy, D. & Liehr, G. (1999) Estrogen, DNA damage and mutations. *Mutat. Res*, **424**, 107–115
- Roy, D. & Singh, K.P. (2004) Estrogen-induced genetic alterations and their role in carcinogenicity. *Curr. Genom.*, **5**, 245–257
- Roy, D., Parkash, J. & Narayan, S. (2004) Genetics and bioenergetics of mitochondria influencing the etiology and pharmacology of steroidal hormones. *Curr. Pharmacogenom.*, **2**, 379–390
- Rubig, A. (2003) Drospirenone: A new cardiovascular-active progestin with antialdosterone and antiandrogenic properties. *Climacteric*, **6** (Suppl. 3), 49–54
- Rylander-Rudqvist, T., Wedrén, S., Jonasdottir, G., Ahlberg, S., Weiderpass, E., Persson, I. & Ingelman-Sundberg, M. (2004) Cytochrome P450 1B1 gene polymorphisms and postmenopausal endometrial cancer risk. *Cancer Epidemiol. Biomarkers Prev.*, **13**, 1515–1520
- Sakamoto, S., Kudo, H., Suzuki, S., Mitamura, T., Sassa, S., Kuwa, K., Chun, Z., Yoshimura, S., Maemura, M., Nakayama, T. & Shinoda, H. (1997a) Additional effects of medroxyprogesterone acetate on mammary tumors in oophorectomized, estrogenized, DMBA-treated rats. *Anticancer Res.*, **17**, 4583–4588

- Sakamoto, S., Mori, T., Shinoda, H., Sassa, S. & Koyama, T. (1997b) Effects of conjugated estrogens with or without medroxyprogesterone acetate on mammary carcinogenesis, uterine adenomyosis and femur in mice. *Acta anat.*, **159**, 204–208
- Salpeter, S.R., Walsh, J.M.E., Greyber, E., Ormiston, T.M. & Salpeter, E.E. (2004) Mortality associated with hormone replacement therapy in younger and older women. *J. gen. intern. Med.*, **19**, 791–804
- Santen, R.J. (2003) Risk of breast cancer with progestins: Critical assessment of current data. *Steroids*, **68**, 953–964
- Sasaki, M., Tanaka, Y., Kaneuchi, M., Sakuragi, N. & Dahiya, R. (2003) CYP1B1 gene polymorphisms have higher risk for endometrial cancer, and positive correlations with estrogen receptor  $\alpha$  and estrogen receptor  $\beta$  expressions. *Cancer Res.*, **63**, 3913–3918
- Sasano, H., Frost, A.R., Saitoh, R., Harada, N., Poutanen, M., Vihko, R., Bulun, S.E., Silverberg, S.G. & Nagura, H. (1996) Aromatase and 17 $\beta$ -hydroxysteroid dehydrogenase type 1 in human breast carcinoma. *J. clin. Endocrinol. Metab.*, **81**, 4042–4046
- Saure, A., Hirvonen, E., Milsom, I., Christensen, A. & Damber, M.-G. (1996) A randomized, double-blind, multicentre study comparing the clinical effects of two sequential estradiol–progestin combinations containing either desogestrel or norethisterone acetate in climacteric women with estrogen deficiency symptoms. *Maturitas*, **24**, 111–118
- Saure, A., Planellas, J., Poulsen, H.K. & Jaszczak, P. (2000) A double-blind, randomized, comparative study evaluating clinical effects of two sequential estradiol–progestogen combinations containing either desogestrel or medroxyprogesterone acetate in climacteric women. *Maturitas*, **34**, 133–142
- Scarabin, P.-Y., Alhenc-Gelas, M., Oger, E. & Plu-Bureau, G. (1999) Hormone replacement therapy and circulating ICAM-1 in postmenopausal women — A randomised controlled trial. *Thromb. Haemost.*, **81**, 673–675
- Schabath, M.B., Wu, X., Vassilopoulou-Sellin, R., Vaporciyan, A.A. & Spitz, M.R. (2004) Hormone replacement therapy and lung cancer risk: A case–control analysis. *Clin. Cancer Res.*, **10**, 113–123
- Schairer, C., Lubin, J., Troisi, R., Sturgeon, S., Brinton, L. & Hoover, R. (2000) Menopausal estrogen and estrogen–progestin replacement therapy and breast cancer risk. *J. Am. med. Assoc.*, **283**, 485–491
- Schindler, A.E., Campagnoli, C., Druckmann, R., Huber, J., Pasqualini, J.R., Schweppe, K.W. & Thijssen, J.H.H. (2003) Classification and pharmacology of progestins. *Maturitas*, **46** (Suppl. 1), 7–16
- Schoonen, W.G.E.J., Dijkema, R., de Ries, R.J.H., Wagenaars, J.L., Joosten, J.W.H., de Gooyer, M.E., Deckers, G.H. & Kloosterboer, H.J. (1998) Human progesterone receptor A and B isoforms in CHO cells. II. Comparison of binding, transactivation and ED<sub>50</sub> values of several synthetic (anti)progestagens *in vitro* in CHO and MCF-7 cells and *in vivo* in rabbits and rats. *J. steroid Biochem. mol. Biol.*, **64**, 157–170
- Schoonen, W.G.E.J., Deckers, G., de Gooijer, M.E., de Ries, R., Mathijssen-Mommers, G., Hamersma, H. & Kloosterboer, H.J. (2000a) Contraceptive progestins. Various 11-substituents combined with four 17-substituents: 17 $\alpha$ -Ethynyl, five- and six-membered spiromethylene ethers or six-membered spiromethylene lactones. *J. steroid Biochem. mol. Biol.*, **74**, 109–123

- Schoonen, W.G.E.J., Deckers, G.H., de Gooijer, M.E., de Ries, R. & Kloosterboer, H.J. (2000b) Hormonal properties of norethisterone, 7 $\alpha$ -methyl-norethisterone and their derivatives. *J. steroid Biochem. mol. Biol.*, **74**, 213–222
- Schumacher, G. & Neuhaus, P. (2001) The physiological estrogen metabolite 2-methoxyestradiol reduces tumor growth and induces apoptosis in human solid tumors. *J. Cancer Res. clin. Oncol.*, **127**, 405–410
- Schumacher, G., Kataoka, M., Roth, J.A. & Mukhopadhyay, T. (1999) Potent antitumor activity of 2-methoxyestradiol in human pancreatic cancer cell lines. *Clin. Cancer Res.*, **5**, 493–499
- Schütze, N., Vollmer, G., Tiemann, I., Geiger, M. & Knuppen, R. (1993) Catecholestrogens are MCF-7 cell estrogen receptor agonists. *J. steroid Biochem. mol. Biol.*, **46**, 781–789
- Schütze, N., Vollmer, G. & Knuppen, R. (1994) Catecholestrogens are agonists of estrogen receptor dependent gene expression in MCF-7 cells. *J. steroid Biochem. mol. Biol.*, **48**, 453–461
- Seed, M., Sands, R.H., McLaren, M., Kirk, G. & Darko, D. (2000) The effect of hormone replacement therapy and route of administration on selected cardiovascular risk factors in postmenopausal women. *Fam. Pract.*, **17**, 479–507
- Seeger, H., Mueck, A.O. & Lippert, T.H. (2000) Effect of norethisterone acetate on estrogen metabolism in postmenopausal women. *Horm. Metab. Res.*, **32**, 436–439
- Seeger, H., Wallwiener, D. & Mueck, A.O. (2003a) Comparison of the effect of progesterone, medroxyprogesterone acetate and norethisterone on the proliferation of human breast cancer cells. *J. Br. Menopause Soc.*, **9**, 36–38
- Seeger, H., Wallwiener, D. & Mueck, A.O. (2003b) The effect of progesterone and synthetic progestins on serum- and estradiol-stimulated proliferation of human breast cancer cells. *Horm. Metab. Res.*, **35**, 76–80
- Sendag, F., Terek, M.C., Ozsener, S., Oztekin, K., Bilgin, O., Bilgen, I. & Memis, A. (2001) Mammographic density changes during different postmenopausal hormone replacement therapies. *Fertil. Steril.*, **76**, 445–450
- Seth, P., Lunetta, K.L., Bell, D.W., Gray, H., Nasser, S.M., Rhei, E., Kaelin, C.M., Iglehart, D.J., Marks, J.R., Garber, J.E., Haber, D.A. & Polyak, K. (2000) Phenol sulfotransferases: Hormonal regulation, polymorphism, and age of onset of breast cancer. *Cancer Res.*, **60**, 6859–6863
- Setiawan, V.W., Hankinson, S.E., Colditz, G.A., Hunter, D.J. & De Vivo, I. (2004) *HSD17B1* gene polymorphisms and risk of endometrial and breast cancer. *Cancer Epidemiol. Biomarkers Prev.*, **13**, 213–219
- Shapiro, S. (2003) Risks of estrogen plus progestin therapy: A sensitivity analysis of findings in the Women's Health Initiative Randomized Controlled Trial. *Climacteric*, **6**, 302–310
- Shelby, M.D., Tice, R.R. & Witt, K.L. (1997) 17- $\beta$ -Estradiol fails to induce micronuclei in the bone marrow cells of rodents. *Mutat. Res.*, **395**, 89–90
- Shields-Botella, J., Duc, I., Duranti, E., Puccio, F., Bonnet, P., Delansorne, R. & Paris, J. (2003) An overview of nomegestrol acetate selective receptor binding and lack of estrogenic action on hormone-dependent cancer cells. *J. steroid Biochem. mol. Biol.*, **87**, 111–122
- Shimada, T., Watanabe, J., Kawajiri, K., Sutter, T.R., Guengerich, F.P., Gillam, E.M. & Inoue, K. (1999) Catalytic properties of polymorphic human cytochrome P450 1B1 variants. *Carcinogenesis*, **20**, 1607–1613
- Shumaker, S.A., Legault, C., Rapp, S.R., Thal, L., Wallace, R.B., Ockene, J.K., Hendrix, S.L., Jones, B.N., III, Assaf, A.R., Jackson, R.D., Kotchen, J.M., Wassertheil-Smoller, S. & Wactawski-Wende, J. for the WHIMS Investigators (2003) Estrogen plus progestin and the



- incidence of dementia and mild cognitive impairment in postmenopausal women. The Women's Health Initiative Memory Study: A randomized controlled trial. *J. Am. med. Assoc.*, **289**, 2651–2662
- Shumaker, S.A., Legault, C., Kuller, L., Rapp, S.R., Thal, L., Lane, D.S., Fillit, H., Stefanick, M.L., Hendrix, S.L., Lewis, C.E., Masaki, K. & Coker, L.H. for the Women's Health Initiative Memory Study Investigators (2004) Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women. Women's Health Initiative Memory Study. *J. Am. med. Assoc.*, **291**, 2947–2958
- Silvestri, A., Gebara, O., Vitale, C., Wajngarten, M., Leonardo, F., Ramires, J.A.F., Fini, M., Mercurio, G. & Rosano, G.M. (2003) Increased levels of C-reactive protein after oral hormone replacement therapy may not be related to an increased inflammatory response. *Circulation*, **107**, 3165–3169
- Simon, J.A., Hsia, J., Cauley, J.A., Richards, C., Harris, F., Fong, J., Barrett-Connor, E. & Hulley, S.B. (2001a) Postmenopausal hormone therapy and risk of stroke: The Heart and Estrogen-Progestin Replacement Study (HERS). *Circulation*, **103**, 638–642
- Simon, J.A., Hunninghake, D.B., Agarwal, S.K., Lin, F., Cauley, J.A., Ireland, C.C. & Pickar, J.H. for the Heart and Estrogen/Progestin Replacement Study (HERS) Research Group (2001b) Effect of estrogen plus progestin on risk for biliary tract surgery in postmenopausal women with coronary artery disease. *Ann. intern. Med.*, **135**, 493–501
- Singh, K., López-Guerrero, J.A., Llombart-Bosch, A. & Roy, D. (2005) Estrogen-induced mutations and its role in the development of tumorigenesis. In: Li, J.J., Li, S.A. & Llombart-Bosch, A., eds, *Hormonal Carcinogenesis IV*, New York, Springer-Verlag, pp. 475–479
- Sit, A.S., Modugno, F., Weissfeld, J.L., Berga, S.L. & Ness, R.B. (2002) Hormone replacement therapy formulations and risk of epithelial ovarian carcinoma. *Gynecol. Oncol.*, **86**, 118–123
- Sitruk-Ware, R. (2002) Progestogens in hormonal replacement therapy: New molecules, risks, and benefits. *Menopause*, **9**, 6–15
- Sitruk-Ware, R. (2004a) Pharmacological profile of progestins. *Maturitas*, **47**, 277–283
- Sitruk-Ware, R. (2004b) New progestogens: A review of their effects in perimenopausal and postmenopausal women. *Drugs Aging*, **21**, 865–883
- Sitruk-Ware, R., Small, M., Kumar, N., Tsong, Y.Y., Sundaram, K. & Jackanicz, T. (2003) Nestorone: Clinical applications for contraception and HRT. *Steroids*, **68**, 907–913
- Smart, J. & Daly, A.K. (2000) Variation in induced CYP1A1 levels: Relationship to CYP1A1, Ah receptor and *GSTM1* polymorphisms. *Pharmacogenetics*, **10**, 11–24
- Smid-Koopman, E., Kuhne, L.C.M., Hanekamp, E.E., Gielen, S.C.J.P., De Ruiter, P.E., Grootegoed, J.A., Helmerhorst, T.J.M., Burger, C.W., Brinkmann, A.O., Huikeshoven, F.J. & Blok, L.J. (2005) Progesterone-induced inhibition of growth and differential regulation of gene expression in PRA- and/or PRB-expressing endometrial cancer cell lines. *J. Soc. gynecol. Invest.*, **12**, 285–292
- Smith, D.C., Prentice, R., Thompson, D.J. & Herrmann, W.L. (1975) Association of exogenous estrogen and endometrial carcinoma. *New Engl. J. Med.*, **293**, 1164–1167
- Smith, E.M., Johnson, S.R., Figuerres, E.J., Mendoza, M., Feddersen, D., Haugen, T.H. & Turek, L.P. (1997) The frequency of human papillomavirus detection in postmenopausal women on hormone replacement therapy. *Gynecol. Oncol.*, **65**, 441–446

- Spink, B.C., Katz, B.H., Hussain, M.M., Pang, S., Connor, S.P., Aldous, K.M., Gierthy, J.F. & Spink, D.C. (2000) SULT1A1 catalyzes 2-methoxyestradiol sulfonation in MCF-7 breast cancer cells. *Carcinogenesis*, **21**, 1947–1957
- Stafford, R.S., Saglam, D., Causino, N. & Blumenthal, D. (1998) The declining impact of race and insurance status on hormone replacement therapy. *Menopause*, **5**, 140–144
- Stahlberg, C., Pedersen, A.T., Lynge, E., Andersen, Z.J., Keiding, N., Hundrup, Y.A., Obel, E.B. & Ottesen, B. (2004) Increased risk of breast cancer following different regimens of hormone replacement therapy frequently used in Europe. *Int. J. Cancer*, **109**, 721–727
- Stampfer, M.J. & Colditz, G.A. (1991) Estrogen replacement therapy and coronary heart disease: A quantitative assessment of the epidemiologic evidence. *Prev. Med.*, **20**, 47–63
- Stefanick, M.L., Cochrane, B.B., Hsia, J., Barad, D.H., Liu, J.H. & Johnson, S.R. (2003) The Women's Health Initiative postmenopausal hormone trials: Overview and baseline characteristics of participants. *Ann. Epidemiol.*, **13**, S78–S86
- Stice, S.L., Ford, S.P., Rosazza, J.P. & Van Orden, D.E. (1987) Role of 4-hydroxylated estradiol in reducing Ca<sup>2+</sup> uptake of uterine arterial smooth muscle cells through potential-sensitive channels. *Biol. Reprod.*, **36**, 361–368
- Stoilov, I., Akarsu, A.N., Alozie, I., Child, A., Barsoum-Homsy, M., Turacli, M.E., Or, M., Lewis, R.A., Ozdemir, N., Brice, G., Aktan, S.G., Chevrette, L., Coca-Prados, M. & Sarfarazi, M. (1998) Sequence analysis and homology modeling suggest that primary congenital glaucoma on 2p21 results from mutations disrupting either the hinge region or the conserved core structures of cytochrome P4501B1. *Am. J. Hum. Genet.* **62**, 573–584
- Strickler, R.C. (2003) Women's Health Initiative results: A glass more empty than full. *Fertil. Steril.*, **80**, 488–490
- Strothmann, A. & Schneider, H.P.G. (2003) Hormone therapy: The European women's perspective. *Climacteric*, **6**, 337–346
- Sturdee, D.W., Ulrich, L.G., Barlow, D.H., Wells, M., Campbell, M.J., Vessey, M.P., Nielsen, B., Anderson, M.C. & Bragg, A.J. (2000) The endometrial response to sequential and continuous combined oestrogen-progestogen replacement therapy. *Br. J. Obstet. Gynaecol.*, **107**, 1392–1400
- Sudhir, K., Chou, T.M., Mullen, W.L., Hausmann, D., Collins, P., Yock, P.G. & Chatterjee, K. (1995) Mechanisms of estrogen-induced vasodilation: In vivo studies in canine coronary conductance and resistance arteries. *J. Am. Coll. Cardiol.*, **26**, 807–814
- Suparto, I.H., Williams, J.K., Cline, J.M., Anthony, M.S. & Fox, J.L. (2003) Contrasting effects of two hormone replacement therapies on the cardiovascular and mammary gland outcomes in surgically postmenopausal monkeys. *Am. J. Obstet. Gynecol.*, **188**, 1132–1140
- Suvanto-Luukkonen, E., Malinen, H., Sundström, H., Penttinen, J. & Kauppila, A. (1998) Endometrial morphology during hormone replacement therapy with estradiol gel combined to levonorgestrel-releasing intrauterine device or natural progesterone. *Acta obstet. gynecol. scand.*, **77**, 758–763
- Suzuki, T., Moriya, T., Ariga, N., Kaneko, C., Kanazawa, M. & Sasano, H. (2000) 17β-Hydroxysteroid dehydrogenase type 1 and type 2 in human breast carcinoma: A correlation to clinicopathological parameters. *Br. J. Cancer*, **82**, 518–523
- Suzuki, T., Nakata, T., Miki, Y., Kaneko, C., Moriya, T., Ishida, T., Akinaga, S., Hirakawa, H., Kimura, M. & Sasano, H. (2003) Estrogen sulfotransferase and steroid sulfatase in human breast carcinoma. *Cancer Res.*, **63**, 2762–2770

- Syvänen, A.-C., Tilgmann, C., Rinne, J. & Ulmanen, I. (1997) Genetic polymorphism of catechol-O-methyltransferase (COMT): Correlation of genotype with individual variation of S-COMT activity and comparison of the allele frequencies in the normal population and Parkinsonian patients in Finland. *Pharmacogenetics*, **7**, 65–71
- Tagawa, H., Shimokawa, H., Tagawa, T., Kuroiwa-Matsumoto, M., Hirooka, Y. & Takeshita, A. (1997) Short-term estrogen augments both nitric oxide-mediated and non-nitric oxide-mediated endothelium-dependent forearm vasodilation in postmenopausal women. *J. cardiovascular. Pharmacol.*, **30**, 481–488
- Tang, Y.M., Green, B.L., Chen, G.F., Thompson, P.A., Lang, N.P., Shinde, A., Lin, D.X., Tan, W., Lyn-Cook, B.D., Hammons, G.J. & Kadlubar, F.F. (2000) Human *CYP1B1* *Leu*<sup>432</sup>*Val* gene polymorphism: Ethnic distribution in African-Americans, Caucasians and Chinese; oestradiol hydroxylase activity; and distribution in prostate cancer cases and controls. *Pharmacogenetics*, **10**, 761–766
- Teede, H.J., McGrath, B.P., Smolich, J.J., Malan, E., Kotsopoulos, D., Liang, Y.-L. & Peeverill, R.E. (2000) Postmenopausal hormone replacement therapy increases coagulation activity and fibrinolysis. *Arterioscler. Thromb. vasc. Biol.*, **20**, 1404–1409
- Terashima, I., Suzuki, N. & Shibutani, S. (2001) Mutagenic properties of estrogen quinone-derived DNA adducts in simian kidney cells. *Biochemistry*, **40**, 166–172
- Thom, M.H., White, P.J., Williams, R.M., Sturdee, D.W., Paterson, M.E.L., Wade-Evans, T. & Studd, J.W.W. (1979) Prevention and treatment of endometrial disease in climacteric women receiving oestrogen therapy. *Lancet*, **ii**, 455–457
- Thuncke, I., Schulte, H.M. & Bamberger, A.-M. (2000) Biphasic effect of medroxyprogesterone-acetate (MPA) treatment on proliferation and cyclin D1 gene transcription in T47D breast cancer cells. *Breast Cancer Res. Treat.*, **63**, 243–248
- Tikkanen, M.J., Nikkilä, E.A., Kuusi, T. & Sipinen, S.U. (1982) High density lipoprotein-2 and hepatic lipase: Reciprocal changes produced by estrogen and norgestrel. *J. clin. Endocrinol. Metab.*, **54**, 1113–1117
- Tikkanen, M.J., Kuusi, T., Nikkilä, E.A. & Sipinen, S. (1986) Post-menopausal hormone replacement therapy: Effects of progestogens on serum lipids and lipoproteins. A review. *Maturitas*, **8**, 7–17
- Tinley, T.L., Leal, R.M., Randall-Hlubek, D.A., Cessac, J.W., Wilkens, L.R., Rao, P.N. & Mooberry, S.L. (2003) Novel 2-methoxyestradiol analogues with antitumor activity. *Cancer Res.*, **63**, 1538–1549
- Tjønneland, A., Christensen, J., Thomsen, B.L., Olsen, A., Overvad, K., Ewertz, M. & Møller, L. (2004) Hormone replacement therapy in relation to breast carcinoma incidence rate ratios: A prospective Danish cohort study. *Cancer*, **100**, 2328–2337
- Todorovic, R., Devanesan, P., Higginbotham, S., Zhao, J., Gross, M.L., Rogan, E.G. & Cavalieri, E.L. (2001) Analysis of potential biomarkers of estrogen-initiated cancer in the urine of Syrian golden hamsters treated with 4-hydroxyestradiol. *Carcinogenesis*, **22**, 905–911
- Townsend, J. (1998) Hormone replacement therapy: Assessment of present use, costs, and trends. *Br. J. gen. Pract.*, **48**, 955–958
- Troisi, R.J., Schairer, C., Chow, W.-H., Schatzkin, A., Brinton, L.A. & Fraumeni, J.F., Jr (1997) A prospective study of menopausal hormones and risk of colorectal cancer (United States). *Cancer Causes Control*, **8**, 130–138

- Tsutsui, T., Tamura, Y., Hagiwara, M., Miyachi, T., Hikiba, H., Kubo, C. & Barrett, J.C. (2000) Induction of mammalian cell transformation and genotoxicity by 2-methoxyestradiol, an endogenous metabolite of estrogen. *Carcinogenesis*, **21**, 735–740
- Tsutsui, T., Tamura, Y., Yagi, E. & Barrett, J.C. (2000a) Involvement of genotoxic effects in the initiation of estrogen-induced cellular transformation: Studies using Syrian hamster embryo cells treated with 17 $\beta$ -estradiol and eight of its metabolites. *Int. J. Cancer*, **86**, 8–14
- Tsutsui, T., Tamura, Y., Hagiwara, M., Miyachi, T., Hikiba, H., Kubo, C. & Barrett, J.C. (2000b) Induction of mammalian cell transformation and genotoxicity by 2-methoxyestradiol, an endogenous metabolite of estrogen. *Carcinogenesis*, **21**, 735–740
- Tuba, Z., Bardin, C.W., Dancsi, A., Francsics-Czinege, E., Molnar, C., Csorgei, J., Falkay, G., Koide, S.S., Kumar, N., Sundaram, K., Dukat-Abrok, V. & Balogh, G. (2000) Synthesis and biological activity of a new progestogen, 16-methylene-17 $\alpha$ -hydroxy-18-methyl-19-norpregn-4-ene-3,20-dione acetate. *Steroids*, **65**, 266–274
- Tukey, R.H. & Strassburg, C.P. (2000) Human UDP-glucuronosyltransferases: Metabolism, expression, and disease. *Ann. Rev. Pharmacol. Toxicol.*, **40**, 581–616
- Turan, V.K., Sanchez, R.I., Li, J.J., Li, S.A., Reuhl, K.R., Thomas, P.E., Conney, A.H., Gallo, M.A., Kauffman, F.C. & Mesia-Vela, S. (2004) The effects of steroidal estrogens in ACI rat mammary carcinogenesis: 17 $\beta$ -Estradiol, 2-hydroxyestradiol, 4-hydroxyestradiol, 16 $\alpha$ -hydroxyestradiol, and 4-hydroxyestrone. *J. Endocrinol.*, **183**, 91–99
- Turgeon, D., Carrier, J.-S., Lévesque, E., Hum, D.W. & Bélanger, A. (2001) Relative enzymatic activity, protein stability, and tissue distribution of human steroid-metabolizing UGT2B sub-family members. *Endocrinology*, **142**, 778–787
- Tworoger, S.S., Chubak, J., Aiello, E.J., Ulrich, C.M., Atkinson, C., Potter, J.D., Yasui, Y., Stapleton, P.L., Lampe, J.W., Farin, F.M., Stanczyk, F.Z. & McTiernan, A. (2004) Association of *CYP17*, *CYP19*, *CYP11B1*, and *COMT* polymorphisms with serum and urinary sex hormone concentrations in postmenopausal women. *Cancer Epidemiol. Biomarkers Prev.*, **13**, 94–101
- Ursin, G., London, S., Stanczyk, F.Z., Gentschein, E., Paganini-Hill, A., Ross, R.K. & Pike, M.C. (1999) Urinary 2-hydroxyestrone/16 $\alpha$ -hydroxyestrone ratio and risk of breast cancer in postmenopausal women. *J. natl Cancer Inst.*, **91**, 1067–1072
- Ursin, G., Wilson, M., Henderson, B.E., Kolonel, L.N., Monroe, K., Lee, H.-P., Seow, A., Yu, M.C., Stanczyk, F.Z. & Gentschein, E. (2001) Do urinary estrogen metabolites reflect the differences in breast cancer risk between Singapore Chinese and United States African-American and white women? *Cancer Res.*, **61**, 3326–3329
- Ursin, G., London, S., Yang, D., Tseng, C.-C., Pike, M.C., Bernstein, L., Stanczyk, F.Z. & Gentschein, E. (2002) Urinary 2-hydroxyestrone/16 $\alpha$ -hydroxyestrone ratio and family history of breast cancer in premenopausal women. *Breast Cancer Res. Treat.*, **72**, 139–143
- US Preventive Service Task Force (2002) Postmenopausal hormone replacement therapy for primary prevention of chronic conditions: Recommendations and rationale. *Ann. intern. Med.*, **137**, 834–839
- Utsumi, T., Yoshimura, N., Takeuchi, S., Ando, J., Maruta, M., Maeda, K. & Harada, N. (1999) Steroid sulfatase expression is an independent predictor of recurrence in human breast cancer. *Cancer Res.*, **59**, 377–381
- Utsunomiya, H., Suzuki, T., Kaneko, C., Takeyama, J., Nakamura, J., Kimura, K., Yoshihama, M., Harada, N., Ito, K., Konno, R., Sato, S., Okamura, K. & Sasano, H. (2001) The analyses of

- 17 $\beta$ -hydroxysteroid dehydrogenase isozymes in human endometrial hyperplasia and carcinoma. *J. clin. Endocrinol. Metab.*, **86**, 3436–3443
- Utsunomiya, H., Suzuki, T., Ito, K., Moriya, T., Konno, R., Sato, S., Yaegashi, N., Okamura, K. & Sasano, H. (2003) The correlation between the response to progestogen treatment and the expression of progesterone receptor  $\beta$  and 17 $\beta$ -hydroxysteroid dehydrogenase type 2 in human endometrial carcinoma. *Clin. Endocrinol.*, **58**, 696–703
- Utsunomiya, H., Ito, K., Suzuki, T., Kitamura, T., Kaneko, C., Nakata, T., Niikura, H., Okamura, K., Yaegashi, N. & Sasano, H. (2004) Steroid sulfatase and estrogen sulfotransferase in human endometrial carcinoma. *Clin. Cancer Res.*, **10**, 5850–5856
- Valdivia, I., Campodonico, I., Tapia, A., Capetillo, M., Espinoza, A. & Lavin, P. (2004) Effects of tibolone and continuous combined hormone therapy on mammographic breast density and breast histochemical markers in postmenopausal women. *Fertil. Steril.*, **81**, 617–623
- Vallée, M., Albert, C., Beaudry, G., Hum, D.W. & Bélanger, A. (2001) Isolation and characterization of the monkey UDP-glucuronosyltransferase cDNA clone monUGT1A01 active on bilirubin and estrogens. *J. steroid Biochem. mol. Biol.*, **77**, 239–249
- Venkov, C.D., Rankin, A.B. & Vaughan, D.E. (1996) Identification of authentic estrogen receptor in cultured endothelial cells. *Circulation*, **94**, 727–733
- Vestergaard, P., Hermann, A.P., Stilgren, L., Tofteng, C.L., Sorensen, O.H., Eiken, P., Nielsen, S.P. & Mosekilde, L. (2003) Effects of 5 years of hormonal replacement therapy on menopausal symptoms and blood pressure — A randomised controlled study. *Maturitas*, **46**, 123–132
- Vihma, V., Adlercreutz, H., Tiitinen, A., Kiuru, P., Wähälä, K. & Tikkanen, M.J. (2001) Quantitative determination of estradiol fatty acid esters in human pregnancy serum and ovarian follicular fluid. *Clin. Chem.*, **47**, 1256–1262
- Vihma, V., Tiitinen, A., Ylikorkala, O. & Tikkanen, M.J. (2003a) Quantitative determination of estradiol fatty acid esters in lipoprotein fractions in human blood. *J. clin. Endocrinol. Metab.*, **88**, 2552–2555
- Vihma, V., Vehkavaara, S., Yki-Järvinen, H., Hohtari, H. & Tikkanen, M.J. (2003b) Differential effects of oral and transdermal estradiol treatment on circulating estradiol fatty acid ester concentrations in postmenopausal women. *J. clin. Endocrinol. Metab.*, **88**, 588–593
- Viscoli, C.M., Brass, L.M., Kernan, W.N., Sarrel, P.M., Suissa, S. & Horwitz, R.I. (2001) A clinical trial of estrogen-replacement therapy after ischemic stroke. *New Engl. J. Med.*, **345**, 1243–1249
- Vitale, C., Fini, M., Leonardo, F., Rossini, P., Cerquetani, E., Onorati, D. & Rosano, G.M.C. (2001) Effect of estradiol valerate alone or in association with cyproterone acetate upon vascular function of postmenopausal women at increased risk for cardiovascular disease. *Maturitas*, **40**, 239–245
- Voigt, L.F., Weiss, N.S., Chu, J., Daling, J.R., McKnight, B. & van Belle, G. (1991) Progestagen supplementation of exogenous oestrogens and risk of endometrial cancer. *Lancet*, **338**, 274–277
- Volterrani, M., Rosano, G., Coats, A., Beale, C. & Collins, P. (1995) Estrogen acutely increases peripheral blood flow in postmenopausal women. *Am. J. Med.*, **99**, 119–122
- Von Schoultz, B. (2003) Clinical efficacy and safety of combined estradiol valerate and dienogest: A new no-bleed treatment. *Climacteric*, **6** (Suppl. 2), 24–32
- Wahab, M., Thompson, J., Hamid, B., Deen, S. & Al-Azzawi, F. (1999) Endometrial histomorphometry of trimegestone-based sequential hormone replacement therapy: A weighted comparison with the endometrium of the natural cycle. *Hum. Reprod.*, **14**, 2609–2618

- Walsh, B.W., Schiff, I., Rosner, B., Greenberg, L., Ravnikar, V. & Sacks, F.M. (1991) Effects of postmenopausal estrogen replacement on the concentrations and metabolism of plasma lipoproteins. *New Engl. J. Med.*, **325**, 1196–1204
- Walsh, B.W., Paul, S., Wild, R.A., Dean, R.A., Tracy, R.P., Cox, D.A. & Anderson, P.W. (2000) The effects of hormone replacement therapy and raloxifene on C-reactive protein and homocysteine in healthy postmenopausal women: A randomized, controlled trial. *J. clin. Endocrinol. Metab.*, **85**, 214–218
- Wang, Z., Yang, D., Mohanakrishnan, A.K., Fanwick, P.E., Nampoothiri, P., Hamel, E. & Cushman, M. (2000) Synthesis of B-ring homologated estradiol analogues that modulate tubulin polymerization and microtubule stability. *J. med. Chem.*, **43**, 2419–2429
- Wassertheil-Smoller, S., Hendrix, S.L., Limacher, M., Heiss, G., Kooperberg, C., Baird, A., Kotchen, T., Curb, J.D., Black, H., Rossouw, J.E., Aragaki, A., Safford, M., Stein, E., Laowattana, S. & Mysiw, W.J. for the WHI Investigators (2003) Effect of estrogen plus progestin on stroke in postmenopausal women: The Women's Health Initiative: A randomized trial. *J. Am. med. Assoc.*, **289**, 2673–2684
- Watanabe, J., Shimada, T., Gillam, E.M., Ikuta, T., Suemasu, K., Higashi, Y., Gotoh, O. & Kawajiri, K. (2000) Association of CYP1B1 genetic polymorphism with incidence to breast and lung cancer. *Pharmacogenetics*, **10**, 25–33
- Wathen, C.N., Feig, D.S., Feightner, J.W., Abramson, B.L., Cheung, A.M. & the Canadian Task Force on Preventive Health Care (2004) Hormone replacement therapy for the primary prevention of chronic diseases: Recommendation statement from the Canadian Task Force on Preventive Health Care. *Can. med. Assoc. J.*, **170**, 1535–1537
- Weiderpass, E., Adami, H.-O., Baron, J.A., Magnusson, C., Bergstrom, R., Lindgren, A., Correia, N. & Persson, I. (1999) Risk of endometrial cancer following estrogen replacement with and without progestins. *J. natl Cancer Inst.*, **91**, 1131–1137
- van de Weijer, P.H.M., Scholten, P.C., van der Mooren, M.J., Barentsen, R. & Kenemans, P. (1999) Bleeding patterns and endometrial histology during administration of low-dose estradiol sequentially combined with dydrogesterone. *Climacteric*, **2**, 101–109
- Weiss, L.K., Burkman, R.T., Cushing-Haugen, K.L., Voigt, L.F., Simon, M.S., Daling, J.R., Norman, S.A., Bernstein, L., Ursin, G., Marchbanks, P.A., Strom, B.L., Berlin, J.A., Weber, A.L., Doody, D.R., Wingo, P.A., McDonald, J.A., Malone, K.E., Folger, S.G. & Spirtas, R. (2002) Hormone replacement therapy regimens and breast cancer risk. *Obstet. Gynecol.*, **100**, 1148–1158
- Weisz, J., Fritz-Wolz, G., Gestl, S., Clawson, G.A., Creveling, C.R., Liehr, J.G. & Dabbs, D. (2000) Nuclear localization of catechol-*O*-methyltransferase in neoplastic and nonneoplastic mammary epithelial cells. *Am. J. Pathol.*, **156**, 1841–1848
- Wells, M., Sturdee, D.W., Barlow, D.H., Ulrich, L.G., O'Brien, K., Campbell, M.J., Vessey, M.P. & Bragg, A.J. (2002) Effect on endometrium of long term treatment with continuous combined oestrogen-progestogen replacement therapy: Follow up study. *Br. med. J.*, **325**, 239–242
- Wen, W., Cai, Q., Shu, X.O., Cheng, J.R., Parl, F., Pierce, L., Gao, Y.-T. & Zheng, W. (2005) Cytochrome P450 1B1 and catechol-*O*-methyltransferase genetic polymorphisms and breast cancer risk in Chinese women: Results from the Shanghai Breast Cancer Study and a meta-analysis. *Cancer Epidemiol. Biomarkers Prev.*, **14**, 329–335

- Whitehead, M.I., Townsend, P.T., Pryse-Davies, J., Ryder, T.A. & King, R.J.B. (1981) Effects of estrogens and progestins on the biochemistry and morphology of the postmenopausal endometrium. *New Engl. J. Med.*, **305**, 1599–1605
- Wiebe, J.P., Muzia, D., Hu, J., Szwajcer, D., Hill, S.A. & Seachrist, J.L. (2000) The 4-pregnene and 5 $\alpha$ -pregnane progesterone metabolites formed in nontumorous and tumorous breast tissue have opposite effects on breast cell proliferation and adhesion. *Cancer Res.*, **60**, 936–943
- Wiegatz, I. & Kuhl, H. (2004) Progestogen therapies: Differences in clinical effects? *Trends Endocrinol. Metab.*, **15**, 277–285
- Wiklund, I., Karlberg, J. & Mattsson, L.-A. (1993) Quality of life of postmenopausal women on a regimen of transdermal estradiol therapy: A double-blind placebo-controlled study. *Am. J. Obstet. Gynecol.*, **168**, 824–830
- Williams, J.K., Adams, M.R. & Klopfenstein, H.S. (1990) Estrogen modulates responses of atherosclerotic coronary arteries. *Circulation*, **81**, 1680–1687
- Williams, J.K., Honoré, E.K., Washburn, S.A. & Clarkson, T.B. (1994) Effects of hormone replacement therapy on reactivity of atherosclerotic coronary arteries in cynomolgus monkeys. *J. Am. Coll. Cardiol.*, **24**, 1757–1761
- Williams, J.K., Anthony, M.S., Honore, E.K., Herrington, D.M., Morgan, T.M., Register, T.C. & Clarkson, T.B. (1995) Regression of atherosclerosis in female monkeys. *Arterioscler. Thromb. vasc. Biol.*, **15**, 827–836
- Wilson, P.D., Faragher, B., Butler, B., Bu'lock, D., Robinson, E.L. & Brown, A.D.G. (1987) Treatment with oral piperazine oestrone sulphate for genuine stress incontinence in postmenopausal women. *Br. J. Obstet. Gynaecol.*, **94**, 568–574
- Wilson, P.W.F., D'Agostino, R.B., Sullivan, L., Parise, H. & Kannel, W.B. (2002) Overweight and obesity as determinants of cardiovascular risk: The Framingham experience. *Arch. intern. Med.*, **162**, 1867–1872
- Winneker, R.C., Bitran, D. & Zhang, Z. (2003) The preclinical biology of a new potent and selective progestin: Trimegestone. *Steroids*, **68**, 915–920
- Women's Health Initiative Steering Committee (2004) Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The Women's Health Initiative Randomized Controlled Trial. *J. Am. med. Assoc.*, **291**, 1701–1712
- Women's Health Initiative Study Group (1998) Design of the Women's Health Initiative clinical trial and observational study. *Control clin. Trials.*, **19**, 61–109
- Wright, T.C., Holinka, C.F., Ferency, A., Gatsonis, C.A., Mutter, G.L., Nicosia, S. & Richart, R.M. (2002) Estradiol-induced hyperplasia in endometrial biopsies from women on hormone replacement therapy. *Am. J. surg. Pathol.*, **26**, 1269–1275
- Writing Group for the PEPI Trial (1995) Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *J. Am. med. Assoc.*, **273**, 199–208
- Writing Group for the Women's Health Initiative Investigators (2002) Risks and benefits of estrogen plus progestin in healthy premenopausal women. Principal results from the Women's Health Initiative Randomized Controlled Trial. *J. Am. med. Assoc.*, **288**, 321–333
- Wu, A.H., Seow, A., Arakawa, K., Van Den Berg, D., Lee, H.-P. & Yu, M.C. (2003) *HSD17B1* and *CYP17* polymorphisms and breast cancer risk among Chinese women in Singapore. *Int. J. Cancer*, **104**, 450–457

- Wu, J., Richer, J., Horwitz, K.B. & Hyder, S.M. (2004) Progesterin-dependent induction of vascular endothelial growth factor in human breast cancer cells: Preferential regulation by progesterone receptor B. *Cancer Res.*, **64**, 2238–2244
- Wuest, J.H., Jr, Dry, T.J. & Edwards, J.E. (1953) The degree of coronary atherosclerosis in bilaterally oophorectomized women. *Circulation*, **7**, 801–809
- Xu, S., Zhu, B.T. & Conney, A.H. (2001a) Stimulatory effect of clofibrate and gemfibrozil administration on the formation of fatty acid esters of estradiol by rat liver microsomes. *J. Pharmacol. exp. Ther.*, **296**, 188–197
- Xu, S., Zhu, B.T., Cai, M.X. & Conney, A.H. (2001b) Stimulatory effect of clofibrate on the action of estradiol in the mammary gland but not in the uterus of rats. *J. Pharmacol. exp. Ther.*, **297**, 50–56
- Yaffe, M.J., Boyd, N.F., Byng, J.W., Jong, R.A., Fishell, E., Lockwood, G.A., Little, L.E. & Trichler, D.L. (1998) Breast cancer risk and measured mammographic density. *Eur. J. Cancer Prev.*, **7**, S47–S55
- Yager, J.D. & Liehr, J.G. (1996) Molecular mechanisms of estrogen carcinogenesis. *Ann. Rev. Pharmacol. Toxicol.*, **36**, 203–232
- Yamamoto, R., Tatsuta, M., Yamamoto, T. & Terada, N. (1996) The later administration of progesterone more rapidly activates dormant mouse mammary tumor cells initiated by 3'-methyl-4-dimethylaminoazobenzene. *Cancer Lett.*, **100**, 41–45
- Yao, J., Chang, M., Li, Y., Pisha, E., Liu, X., Yao, D., Elguindi, E.C., Blond, S.Y. & Bolton, J.L. (2002) Inhibition of cellular enzymes by equine catechol estrogens in human breast cancer cells: Specificity for glutathione S-transferase P1-1. *Chem. Res. Toxicol.*, **15**, 935–942
- Yao, J., Li, Y., Chang, M., Wu, H., Yang, X., Goodman, J.E., Liu, X., Liu, H., Mesecar, A.D., van Breemen, R.B., Yager, D.J. & Bolton, J.L. (2003) Catechol estrogen 4-hydroxyequilenin is a substrate and an inhibitor of catechol-O-methyltransferase. *Chem. Res. Toxicol.*, **16**, 668–675
- Yared, E., McMillan, T.J. & Martin, F.L. (2002) Genotoxic effects of oestrogens in breast cells detected by the micronucleus assay and the Comet assay. *Mutagenesis*, **17**, 345–352
- Yasui, M., Matsui, S., Laxmi, Y.R.S., Suzuki, N., Kim, S.Y., Shibutani, S. & Matsuda, T. (2003) Mutagenic events induced by 4-hydroxyequilin in *supF* shuttle vector plasmid propagated in human cells. *Carcinogenesis*, **24**, 911–917
- Yue, T.-L., Wang, X., Loudon, C.S., Gupta, S., Pillarisetti, K., Gu, J.-L., Hart, T.K., Lysko, P.G. & Feuerstein, G.Z. (1997) 2-Methoxyestradiol, an endogenous estrogen metabolite, induces apoptosis in endothelial cells and inhibits angiogenesis: Possible role for stress-activated protein kinase signaling pathway and Fas expression. *Mol. Pharmacol.*, **51**, 951–962
- Zandi, P.P., Carlson, M.C., Plassman, B.L., Welsh-Bohmer, K.A., Mayer, L.S., Steffens, D.C. & Breitner, J.C.S. for the Cache County Memory Study Investigators (2002) Hormone replacement therapy and incidence of Alzheimer disease in older women. The Cache County Study. *J. Am. med. Assoc.*, **288**, 2123–2129
- Zeller, W.J. & Berger, M.R. (1989) Nicotine and estrogen metabolism — Possible implications of smoking for growth and outcome of treatment of hormone-dependent cancer? Discussion of experimental results. *J. Cancer Res. Oncol.*, **115**, 601–603
- Zhang, Z., Lundeen, S.G., Zhu, Y., Carver, J.M. & Winneker, R.C. (2000) In vitro characterization of trimegestone: A new potent and selective progestin. *Steroids*, **65**, 637–643
- Zhang, F., Swanson, S.M., van Breemen, R.B., Liu, X., Yang, Y., Gu, C. & Bolton, J.L. (2001) Equine estrogen metabolite 4-hydroxyequilenin induces DNA damage in the rat mammary



- tissues: Formation of single-strand breaks, apurinic sites, stable adducts, and oxidized bases. *Chem. Res. Toxicol.*, **14**, 1654–1659
- Zheng, W., Dunning, L., Jin, F. & Holtzman, J. (1998) Correspondence re: G.C. Kabat *et al.*, Urinary estrogen metabolites and breast cancer: A case-control study. *Cancer Epidemiol. Biomarkers Prev.*, **6**, 505–509, 1997. *Cancer Epidemiol. Biomark. Prev.*, **7**, 85–86
- Zheng, W., Xie, D.-W., Jin, F., Cheng, J.-R., Dai, Q., Wen, W.-Q., Shu, X.-O. & Gao, Y.-T. (2000) Genetic polymorphism of cytochrome P450-1B1 and risk of breast cancer. *Cancer Epidemiol. Biomarkers Prev.*, **9**, 147–150
- Zheng, W., Xie, D., Cerhan, J.R., Sellers, T.A., Wen, W. & Folsom, A.R. (2001) Sulfotransferase 1A1 polymorphism, endogenous estrogen exposure, well-done meat intake, and breast cancer risk. *Cancer Epidemiol. Biomarkers Prev.*, **10**, 89–94
- Ziel, H.K. & Finkle, W.D. (1975) Increased risk of endometrial carcinoma among users of conjugated estrogens. *New Engl. J. Med.*, **293**, 1167–1170
- Ziel, H.K., Finkle, W.D. & Greenland, S. (1998) Decline in incidence of endometrial cancer following increase in prescriptions for opposed conjugated estrogens in a prepaid health plan. *Gynecol. Oncol.*, **68**, 253–255