

## EDITORIAL

# Long-term Adjuvant Tamoxifen Therapy and Decreases in Contralateral Breast Cancer

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**Tamoxifen** revolutionized personalized medicine as the first targeted therapy proven to save lives in cancer.<sup>1</sup> The paradigm change proposed to block the breast tumor estrogen receptor (ER), apply long-term adjuvant therapy to block estrogen-stimulated recurrences,<sup>1,2</sup> and apply the potential of

tamoxifen to prevent breast cancer.<sup>3</sup> These strategic recommendations were translated, during the past 3 decades, to clinical care.<sup>4</sup> A meta-analysis<sup>5</sup> of randomized clinical trials revealed that the strategic use of long-term adjuvant tamoxifen therapy is the key to therapeutic success. In addition, we now know that treating metastatic breast cancer (MBC) is only palliative at the end of life, but the same medicine saves lives if applied as long-term adjuvant therapy. Nevertheless, the question has to be asked whether the results would be the same outside the clinical trials process.

The report in this issue of *JAMA Oncology* by Gierach and coworkers<sup>6</sup> is reassuring because all the rules derived, until now, from randomized clinical trial overview analyses hold true.<sup>6</sup> The authors<sup>6</sup> performed a retrospective cohort study of contralateral breast cancer (CBC) in a population of 7541 patients from the records at Kaiser Permanente Northwest and Colorado from 1990 to 2008 and followed up through 2011. The median range of observation was 6.3 years, and 248 patients were identified to have developed CBC. Both tamoxifen and aromatase inhibitors reduced CBC, and longer adjuvant therapy proved to be more beneficial than shorter therapy. The authors<sup>6</sup> estimate that 4 or more years of adjuvant tamoxifen therapy will prevent 3 CBCs per 100 women by 10 years after first diagnosis of ER-positive breast cancer. The authors<sup>6</sup> stress that patients with breast cancer who are undergoing long-term adjuvant endocrine therapy should be encouraged to complete the full course. Indeed, this conclusion is even more important because in the future adjuvant endocrine therapy will last for 10 years.<sup>7-9</sup> However, the challenge is adherence. Simply stated, no medicine, no benefit. A previous report<sup>10</sup> calculates the number of deaths caused by nonadherence with adjuvant tamoxifen therapy. Low adherence results in early recurrence, increased medical costs, and a much worse quality of life.<sup>10</sup>

Gierach and coworkers<sup>6</sup> report the persistence of the protective effects of adjuvant tamoxifen after treatment stops on CBC risk and that this effect is dependent on the duration of tamoxifen therapy. The authors<sup>6</sup> cite a Danish study<sup>11</sup> that found that current users of tamoxifen had a reduced risk of CBC,<sup>11</sup> but former use of tamoxifen had no effect on CBC. Importantly,

the adjuvant therapy used was only for a short period (median, 1-2.5 years).<sup>11</sup> Persistence of the protective effects of tamoxifen using 5 years of treatment in high-risk populations is noted in the National Surgical Adjuvant Breast and Bowel Project trial<sup>12</sup> to reduce the risk of primary breast cancer in high-risk women. These data<sup>12</sup> are supported by the 96-month follow-up of the International Breast Cancer Intervention Study trial and the 20-year follow-up of the Royal Marsden Breast Cancer Prevention trial.<sup>13</sup> The rule is clear: long-term treatment with tamoxifen (5 years) produces a sustained beneficial effect in preventing breast cancer, whereas short-term therapy does not.

This clinical reality now presents the medical community with a paradox. Tamoxifen is a competitive inhibitor of estrogen action at the tumor ER. However, long-term adjuvant tamoxifen therapy<sup>1-3</sup> must be continuous because failure of tamoxifen to block the tumor ER will result in recurrence. However, this laboratory strategy<sup>3</sup> was not predictive for 5 years of adjuvant therapy. Patients survive without the benefit of tamoxifen blocking the ER to prevent recurrence. Herein lies the paradox. Tamoxifen is not cytotoxic, so where does the cytotoxicity of long-term tamoxifen therapy come from to protect patients after 5 years of adjuvant tamoxifen therapy?

The answer comes from laboratory research on the evolution of acquired resistance to tamoxifen.<sup>14-17</sup> Investigation of ER-positive breast tumors transplanted into tamoxifen-treated ovariectomized athymic mice results in the development of acquired resistance to tamoxifen within 1 to 2 years.<sup>12</sup> Uniquely, breast tumors develop because of tamoxifen treatment not despite tamoxifen treatment, and tumors use tamoxifen or estrogen to maintain tumor growth.<sup>14,17</sup> This biological knowledge is the scientific foundation for using an aromatase inhibitor (to prevent the postmenopausal patient from synthesizing estrogen) or fulvestrant (which destroys the tumor ER as a pure antiestrogen) as second-line therapies for MBC in which tamoxifen treatment has not worked. Antiestrogenic therapy is the strategy of choice because estrogen stimulates tamoxifen-resistant tumor growth.

Additional transplantation of ER-positive breast tumors with early acquired resistance to tamoxifen into tamoxifen-treated athymic mice for up to 5 years replicates the clinical strategy of 5 years of adjuvant therapy.<sup>11</sup> Tamoxifen-stimulated growth continues, but paradoxically physiologic estrogen has a significant antitumor effect.<sup>11</sup> Estrogen is cytotoxic, and tumors disappear completely. Yao and coworkers<sup>18</sup> proposed 2 clinical applications: (i) physiologic estrogen to treat MBC af-

# Long Term Tamoxifen Treatment For Breast Cancer

**Virgil Craig Jordan**



## **Long Term Tamoxifen Treatment For Breast Cancer:**

**Long-term Tamoxifen Treatment for Breast Cancer** Virgil Craig Jordan, 1994 During the past twenty years tamoxifen has become the most widely prescribed and most successful drug used in the treatment of breast cancer In this volume editor V Craig Jordan provides articles that trace the development pharmacology and clinical research surrounding this drug which by the year 2000 could be used to treat as many as one million women annually Drawing from research conducted by specialists in the United States the United Kingdom and Italy the series of articles describes the clinical testing of tamoxifen highlighting the benefits Studies show that tamoxifen lowers cholesterol and can potentially protect women against osteoporosis and fatal coronary heart disease Equally important is a discussion of side effects and possible drug interactions and how these issues relate to patient concerns An investigation of the development of a new class of drugs for use after tamoxifen fails provides valuable insight into future treatments as the contributors consider possible resistance to tamoxifen This volume provides invaluable information for physicians and surgeons who care for patients with breast cancer and for women interested in exploring this therapeutic dimension **Tamoxifen and Breast Cancer** Michael W.

DeGregorio, Valerie J. Wiebe, 1999-01-01 A discussion of the diagnosis of breast cancer and the risks benefits and limitations of treatment alternatives particularly tamoxifen This edition contains information on developments in the use of tamoxifen especially in the results of the Breast Cancer Prevention Trial Treatment of the Postmenopausal Woman Rogerio A. Lobo, 2007-06-05 For anyone who treats postmenopausal women this latest edition of Rogerio Lobo s classic work combines the best from two well known references Menopause and the second edition of Treatment of the Postmenopausal Woman By adding significant discussions of the basic science behind menopause it is possible to objectively assess the clinical value and limitations of current approaches to treatment and provide a basis and rationale for strategies that will result in better individualized and specialized care Not only does the third edition discuss diagnosis and treatment of menopause but it covers biological anatomical physiological pathobiological and pharmacological aspects as well bringing together in one source all of the information needed to understand and treat postmenopausal conditions Over 50% new material representing the vast amount of information available since the Women s Health Initiative WHI clinical trials were completed making this the most up to date reference on postmenopausal women Includes several new sections on comparisons between clinical trials and observational data urology and pelvic support Each section is preceded by a preface to put the area into context with many chapters having suggested treatment regimens *Biological and Hormonal Therapies of Cancer* Kenneth A. Foon, Hyman B. Muss, 1998-01-31 This volume Biological and Hormonal Therapies of Cancer which is part of the series Cancer Treatment and Research presents selected new information concerning biologic and hormonal therapy of cancer We have attempted to provide the reader with topics of major interest in a timely fashion There is renewed interest in biologic therapy of cancer Two chapters review the role of interferon in the hematologic malignancies and in solid tumors Vaccine

therapies have come to the forefront of cancer therapy recently and two chapters approach different strategies of vaccine therapies one reviews the cellular vaccine therapies and another the anti idotype approach The hormonal therapy chapters focus on current uses of endocrine therapy in endometrial breast and prostate cancer In addition hormonal strategies for the prevention of breast cancer and endometrial cancer including exciting information relating to phytochemicals are presented The effects of tamoxifen on endometrium is a topic of major interest and is discussed in detail Finally there is a chapter on estrogen receptor expression and regulation in human breast cancer These chapters are all written by experts in the field and contain timely and relevant information of interest to laboratory and clinical scientists and practitioners alike Biologic and endocrine therapies represent major areas of cancer research interest The advent of newer biologic therapies including new antibody targeted treatments and the use of biologics as tumor modulators to enhance the effects of other treatment regimens is an exploding avenue of research

**Tamoxifen Tales** V. Craig Jordan, 2022-01-12 Tamoxifen Tales Suggestions for Scientific Survival presents a case study describing the academic journey of teams behind major advances in medical sciences highlighting lessons learned that are applicable to the next generation of scientists This book provides a manual on the successful mentoring of young scientists including stories describing how training experience shaped careers to become leaders in academia and the pharmaceutical industry The book documents Professor V Craig Jordan's 50 year career in medical sciences that led to the discovery and development of Selective Estrogen Receptor Modulators SERMs which became the standard of women's healthcare around the world Additionally it illustrates the versatility of a scientist with a commitment to serving societies This important resource will be a useful and interesting book for established medical scientists research mentors and advanced students wanting to chart a successful and impactful research career Highlights lessons learned from the journey behind discovery science that are applicable to the scientific journey of the next generation of scientists Provides a manual on the successful mentoring of young scientists to become leaders in academia and the pharmaceutical industry Examines cancer treatment based on a personal determination to challenge at the frontiers of the science and to relate to personal life experience Includes references for further research reading Journal of the National Cancer Institute, 1990

**Meyler's Side Effects of Endocrine and Metabolic Drugs** Jeffrey K. Aronson, 2009-02-21 Elsevier now offers a series of derivative works based on the acclaimed Meyler's Side Effect of Drugs 15th Edition These individual volumes are grouped by specialty to benefit the practicing physician or health care clinician Endocrine and metabolic diseases are common includes diseases such as diabetes thyroid disease and obesity Endocrinologists including diabetes professionals internal medicine and primary care practitioners obstetricians and gynecologists and others will find this book useful when treating endocrine or metabolic diseases The material is drawn from the 15th edition of the internationally renowned encyclopedia Meyler's Side Effects of Drugs and the latest volumes in the companion series Side Effects of Drugs Annuals Drug names have usually been designated by their recommended or proposed International Non

proprietary Names rINN or pINN when those are not available clinical names have been used In some cases brand names have been used This volume is critical for any health professional involved in the administration of endocrine and metabolics mediations Surpasses the Physician s Desk Reference by including clinical case studies and independent expert analysis Complete index of drug names Most complete cross referencing of drug drug interactions available Extensive references to primary and secondary literature Also includes information on adverse effects in pregnancy The book is divided into eight sections Corticosteroids and related drugs Prostaglandins Sex hormones and related drugs Iodine and drugs that affect thyroid function Insulin and other hypoglycemic drugs Other hormones and related drugs Lipid regulated drugs Endocrine and metabolic adverse effects of non hormonal and non metabolic drugs *Cumulated Index Medicus* ,1996 **Yen & Jaffe's Reproductive Endocrinology E-Book** Jerome F. Strauss,Robert L. Barbieri,2009-06-02 Thoroughly revised and now enhanced with color artwork the new edition of this premier reference continues to offer the latest information on the diagnosis and management of reproductive endocrine disorders National and international leaders from the field of reproductive endocrinology including 30 new authors equip you with coverage that encompasses the full spectrum of reproductive pathophysiology and disorders from pregnancy and birth to reproductive aging Full color illustrations and new drawings provide a real life depiction of basic cell structures and endocrine responses for a better understanding of the material while new chapters explore the issues shaping today s practice Covers the full spectrum of reproductive pathophysiology and disorders from pregnancy and birth to reproductive aging Includes the work of leaders in the field of reproductive endocrinology for guidance you can trust Offers new content on preservation of fertility endocrine disturbances affecting reproduction imaging technologies and adolescent reproductive endocrinology that explore the issues shaping today s practice Includes full color illustrations and new drawings which provide a real life depiction of anatomy and cell function and dysfunction for a greater understanding Provides a list of suggested readings at the end of each chapter for further reference Presents fresh insights into today s field and future advances as well as a greater international perspective

**Drug Therapy in Nursing** Diane S. Aschenbrenner,Samantha J. Venable,2009 This text presents a totally nursing focused framework for teaching and learning nursing pharmacology and places the patient at the center of all drug administration decisions and considerations The book presents core drug knowledge using prototypes of different drug classes and emphasizes core patient variables that influence the patient s response to therapy This thoroughly updated Third Edition covers newly approved drugs has separate chapters on drugs affecting fungal and viral infections and includes more pathophysiology information FDA Black Box warnings have been added to the discussion of each prototype when applicable and safety alerts have been added to emphasize prevention of common medication errors A companion Website offers student and instructor ancillaries including NCLEX style questions pathophysiology animations medication administration videos and dosage calculation quizzes *Holland-Frei Cancer Medicine 8* James F. Holland,2010 Holland Frei Cancer

Medicine serves as a quick reference to current information on an extensive list of cancers including breast lung thyroid colorectal ovarian prostate and gastric cancer to name but a few Presented as an accessible pocket sized handbook the chapters are organized in an outline format offering only the most essential information on the etiology staging including TNM staging and treatment for each cancer type Individual chapters are devoted to the molecular biology of cancer cancer prevention cancer screening the mechanisms of chemotherapy and diagnostic imaging in cancer Additionally each chapter lists all the major phase III clinical trials and therefore serves as an excellent reference of the major randomized controlled trials for each cancer reported to date Specific chapters are also dedicated to the discussion of oncologic emergencies pain and palliation and prescription complications At the conclusion of the book a glossary of oncologic terms and chemotherapeutic drug programs a table of common cancer incidences and an overview of the mechanisms common uses and related toxicities of various anti cancer agents are featured In addition performance status tables mathematical formulas and a listing of common biomedical cancer web sites are highlighted

*Cardiotoxicity of Non-Cardiovascular Drugs* Giorgio Minotti, 2010-03-25 Some drugs which are not aimed at treating heart disease have nevertheless been found to have profound effects on heart muscle Cardiotoxicity is one of the major forms of toxicity seen in drugs and it accounts for most drug recalls and delays experienced in regulatory approvals In recent years a number of non cardiac blockbuster drugs such as terfenadine have been withdrawn from major markets because of cardiotoxicity concerns while other drugs have either been withdrawn prior to marketing or required labelling changes that significantly restricted their use In *Cardiotoxicity of Non Cardiovascular Drugs* international experts describe the molecular mechanisms and clinical read outs of cardiac events induced by a broad variety of noncardiovascular drugs Particular emphasis is paid to the preclinical screening of drug cardiotoxicity Topics include metabolic targets of cardiotoxicity regulatory aspects translating molecular mechanisms into clinical trials structure activity relationships in arrhythmias by antihistamines and psychoactive drugs cardiovascular toxicity of antitumor drugs cardiovascular toxicities of non steroidal anti inflammatory drugs cardiovascular toxicities of antiretroviral therapies *Cardiotoxicity of Non Cardiovascular Drugs* is an essential guide to this important area of drug development It will find a place on the bookshelves of researchers regulators and students in medicinal chemistry drug development pharmacology pharmacy and cardiovascular disease

*Clinical Ocular Toxicology E-Book* Frederick T. Fraunfelder, Frederick W. Fraunfelder, Wiley A. Chambers, 2008-06-12 Written by international authorities in ocular toxicology including the Founder of The National Registry of Drug Induced Side Effects and its current Director this essential resource provides the clinically relevant information you need to effectively diagnose and manage herbal chemical and drug related ocular problems Comprehensive coverage of all drugs generic and trade drug names primary uses ocular and systemic side effects and clinical significance make this book like its best selling predecessor *Drug Induced Ocular Side Effects* the ideal reference for quick on the spot consultation Leaders in the field provide need to know information on all aspects of ocular

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**Osteoporosis** Steven R. Cummings, Felicia Cosman, Sophie A. Jamal, 2002 Until recently considered an inevitable part of aging osteoporosis is typically diagnosed only after a serious complication such as a fracture It is now possible however to diagnose high risk patients beforehand Easily performed noninvasive tests estimate bone mass and patients at risk can be treated with new drugs whose efficacy for fracture reduction has been proven in clinical trials Osteoporosis An Evidence Based Guide to Prevention and Management the newest volume in the acclaimed ACP Women's Health series addresses every important facet of this common disease The latest scientific evidence and the extensive clinical experience of the authors provide essential information on the origins and progress of osteoporosis Treatment options are thoroughly reviewed

Adjuvant Therapy of Breast Cancer IV Hans-Jörg Senn, Richard D. Gelber, Aron Goldhirsch, Beat Thürlimann, 2012-12-06 Advances in breast cancer research achieved through the progress of knowledge and development of new therapies have been translated into improved quality of care for breast cancer patients Clinical investigations and clinical trials have made the largest contribution to the body of knowledge that finds its way to the patient Never before during the past decades of management of breast cancer has there been such a fruitful intellectual cross fertilization of ideas among individuals involved in the generation of hypotheses basic research development of drugs and treatments conduct of clinical trials and statistical evaluation the results of all of which are now translated into progress in clinical care Even issues such as the quality of life of breast cancer patients once the domain for few are now being openly addressed by trials and discussed in a much broader forum The IVth International Conference on the Adjuvant Therapy of Primary Breast Cancer also known as the st Gallen Conference was again attended by more than 800 scientists and clinicians interested in this broad spectrum of breast cancer research and the interactions between such diverse fields of interest and specialties as cancer pathology molecular biology and psychosocial oncology This volume collects findings and conclusions presented at the conference

*Meyler's Side Effects of Drugs* Jeffrey K. Aronson, 2015-10-15 Meyler's Side Effects of Drugs The International Encyclopedia of Adverse Drug Reactions and Interactions Sixteenth Edition Seven Volume Set builds on the success of the 15 previous editions providing an extensively

reorganized and expanded resource that now comprises more than 1 500 individual drug articles with the most complete coverage of adverse reactions and interactions found anywhere Each article contains detailed and authoritative information about the adverse effects of each drug with comprehensive references to the primary literature making this a must have reference work for any academic or medical library pharmacologist regulatory organization hospital dispensary or pharmaceutical company The online version of the book provides an unparalleled depth of coverage and functionality by offering convenient desktop access and enhanced features such as increased searchability extensive internal cross linking and fully downloadable and printable full text HTML or PDF articles Enhanced encyclopedic format with drug monographs now organized alphabetically Completely expanded coverage of each drug with more than 1 500 drug articles and information on adverse reactions and interactions Clearer systematic organization of information for easier reading including case histories to provide perspective on each listing Extensive bibliography with over 40 000 references A must have reference work for any academic or medical library pharmacologist regulatory organization hospital dispensary or pharmaceutical company

**Comprehensive Geriatric Oncology** Lodovico Balducci,Gary H. Lyman,William B. Ershler,Martine Extermann,2004-03-01 Published in 2004 This new edition of Comprehensive Geriatric Oncology still offers an exhaustive review of the biology of cancer and aging of the epidemiologic trends in the country and in the world and of the clinical trials that concern cancer prevention and cancer treatment in the elderly

**Cancer Chemotherapy and Biotherapy** Bruce A. Chabner,Dan L. Longo,2011-12-07 Updated to include the newest drugs and those currently in development this Fifth Edition is a comprehensive reference on the preclinical and clinical pharmacology of anticancer agents Organized by drug class the book provides the latest information on all drugs and biological agents their mechanisms of action interactions with other agents toxicities side effects and mechanisms of resistance The authors explain the rationale for use of drugs in specific schedules and combinations and offer guidelines for dose adjustment in particular situations This edition s introduction includes timely information on general strategies for drug usage the science of drug discovery and development economic and regulatory aspects of cancer drug development and principles of pharmacokinetics Eight new chapters have been added and more than twenty have been significantly revised A companion website includes the fully searchable text and an image bank

*Yen and Jaffe's Reproductive Endocrinology* Jerome Frank Strauss,Robert L. Barbieri,2009-01-01 Thoroughly revised and now enhanced with color artwork this new edition offers the latest information on the diagnosis and management of reproductive endocrine disorders As an Expert Consult title it includes convenient online access to the complete text of the book along with all of the images and references linked to Medline

**Selective Estrogen Receptor Modulators** Andrea Manni,Michael Verderame,2002-01-18 Experimental and clinical researchers from a wide range of disciplines present a wealth of fresh scientific information on the biochemistry molecular biology pharmacology and clinical activity of SERMs The basic science chapters of the book focus with an eye to the development of



the ideal SERM on the complex mechanisms of estrogen action including ligand dependent conformational changes in alpha and beta and the recruitment of co activators and co repressors which modulate the estrogen receptor transcriptional activity and contribute to its crosstalk with growth factor signaling The clinical presentation reviews the data accumulated on currently available SERMs primarily tamoxifen and raloxifene in cancer treatment and prevention as well as their effects on the reproductive vascular skeletal and central nervous systems A tentative approach to menopause related health issues is also provided for women with and without a previous diagnosis of localized breast cancer

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