Cardiovascular effects and pattern of use of antineoplastic therapies in female breast cancer patients

By

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ABSTRACT

Cancer survivors are at greater risk of cardiovascular diseases in comparison to the general population. Cardiovascular disorders are among the most prominent comorbidities in breast cancer patients. In order to gain a better understanding of the prescribing practices and cardiovascular risks associated with oncology drugs, this thesis encompasses a detailed review of the molecular and physiological mechanisms leading to drug-induced cardiotoxicity and an evaluation of the cardiovascular risks associated with cancer drug therapies. Using a nested case-control design, we evaluated whether these cancer drugs were associated with adverse cardiovascular outcomes under real-world conditions of use. Although only few oncology drugs are indicated for breast cancer treatment, we were interested in prescribing practices and whether breast cancer treatments are restricted to labelled indications. The characterization of prescribing practices provides insights on the range of antineoplastic agents that should be considered in the evaluation of treatment-related adverse reactions such as cardiotoxicity.

We found that selective estrogen receptor modulators demonstrated a better safety profile than aromatase inhibitors based on their mechanism of action on the cardiovascular system. These observations were corroborated by our findings from logistic regression analyses where aromatase inhibitors were associated with a higher risk of heart failure in a heterogeneous population of breast cancer patients. We reported that off-label

prescribing is common strategy in breast cancer treatment. While this practice tends to be associated with specific socio-demographic and disease characteristics, the majority of off-label encounters are evidence-based decisions. Because these off-label treatments have their own inherent safety profiles, a comprehensive approach, covering all antineoplastic agents administered should be adopted in the evaluation of breast cancer treatment-induced cardiotoxicity. Careful monitoring of patients is crucial for the early detection of warning signs of cardiotoxicity to prevent long-term deleterious effects.

The information contained in this thesis provides useful considerations for the prospective surveillance of cancer drug-induced cardiac events. These findings point to the need for a multi-disciplinary approach to facilitate the rapid diagnosis and treatment of cardiac complications secondary to cancer therapy and to ensure that treatment decisions will maximize tumor response while minimizing adverse outcomes.

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LIST OF ABBREVIATIONS

5-FU	5-Fluorouracil
ABCSG 8	Adjuvant Treatment in Patients with Hormone Receptor-positive Breast Cancer with Good to Moderate Differentiation Trial
ABL	Abelson Murine Leukemia Viral Oncogene Homolog 1
AI	Aromatase Inhibitor
AJCC	American Joint Committee on Cancer
AKT	Protein Kinase B
ARNO 95	Effectiveness of Combination of Arimidex and Nolvadex in Adjuvant Therapy of Breast Carcinoma in Post-menopausal Women Trial
ASCO	American Society of Clinical Oncology
ATAC	Arimidex, Tamoxifen, Alone or in Combination Trial
ATP	Adenosine Triphosphate
BC	Breast Cancer
BCR	Breakpoint Cluster Region Protein
BIG 1-98	Breast International Group 1-98 Trial
BRAF	v-RAF Murine Sarcoma Viral Oncogene
c-Fms	Transmembrane Glycoprotein Receptor Tyrosine Kinase
c-MET	Hepatocyte Growth Factor Receptor
CD20	Cluster of Differentiation 20
CD30	Cluster of Differentiation 30
CD33	Cluster of Differentiation 33
CD52	Cluster of Differentiation 52
CDC	Centers for Disease Control and Prevention
CMF	Cyclophosphamide, Methotrexate and Fluorouracil
CTCL	Cutaneous T-Cell Lymphoma
CTLA-4	Cytotoxic T-Lymphocyte Antigen 4

DCIS	Ductal Carcinoma *in situ*
DDR2	Discordin Domain-containing Receptor 2
DHFR	Dihydrofolate Reductase
DNA	Deoxyribonucleic Acid
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EPH2A	Ephrin Receptor A2
ER	Estrogen Receptor
ERα	Estrogen Receptor Alpha
ERβ	Estrogen Receptor Beta
ErbB-2	Avian Erythroblastosis Oncogene B / Human Epidermal Growth Factor Receptor 2
ETs	Estrogen-targeted therapies
FDA	Food and Drug Administration
FGFR	Fibroblast Growth Factor Receptor (1 and 3)
FGPS	Faculty of Graduate and Postdoctoral Studies
FLT-3	Fms-Like Tyrosine Kinase-3
FSH	Follicle-Stimulating Hormone
GIST	Gastrointestinal Stromal Tumor
GnRH	Gonadotropin-Releasing Hormone
HDAC	Histone deacetylase
HDL	High-Density Lipoprotein
Her-2	Human Epidermal Growth Factor Receptor 2 / Avian Erythroblastosis Oncogene B
hERG	Human Ether-a-go-go-Related Gene
HF	Heart Failure
HRT	Hormone Replacement Therapy
IBCSG	International Breast Cancer Study Group
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification

IGFR	Insulin Growth Factor Receptor
INF-α	Interferon-Alpha
ITK	Interleukin-2 Receptor Inducible T-Cell Kinase
KIT	Mast/Stem Cell Growth Factor Receptor/Cluster of Differentiation 117
LCK	Leukocyte-Specific Protein Tyrosine Kinase
LH	Luteinizing Hormone
LDL	Low-Density Lipoprotein
mTOR	Mammalian Target of Rapamycin
MI	Myocardial Infarction
NCCN	National Comprehensive Cancer Network
NOS	Not Otherwise Specified
NSCLC	Non-Small Cell Lung Carcinoma
OR	Odds Ratio
PARP	Poly ADP Ribose Polymerase
PH	Philadelphia Chromosome
PI3K	Phosphoinositide 3-Kinase
PDGFR	Platelet-Derived Growth Factor Receptor (α and β)
PR	Progesterone Receptor
PTC	Papillary Thyroid Cancer
PTCL	Peripheral T-Cell Lymphoma
PTK5	Fyn-Related Kinase-5
R-CT	Randomized Clinical Trial
RAF-1	Proto-Oncogene Serine/Threonine-Protein Kinase
RET	Glial Cell-Line Derived Neurotrophic Factor Receptor
RNA	Ribonucleic acid
SAPK2	Stress-Activated Protein Kinase 2
SCF	Stem Cell Factor
SERM	Selective Estrogen Receptor Modulator
SERM/DR	Selective Estrogen Receptor Modulator and Down-regulator

SMO	Smoothened Receptor
TIE2	Endothelial-Specific Receptor Tyrosine Kinase 2
TopI1	Topoisomerase I inhibitor
TopI2	Topoisomerase II inhibitor
TrkA	High Affinity Nerve Growth Factor Receptor
TSC	Tuberous sclerosis complex
US	United States of America
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular endothelial growth factor receptor (1, 2 and 3)
WHI	Women's Health Initiative

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PREFACE

In accordance with the thesis regulations of the Faculty of Graduate and Postdoctoral Studies (FGPS), this thesis consists of one manuscript submitted for publication and two manuscripts in the process of being submitted. Each manuscript is prefaced with a brief description and statement of contribution of collaborators and co-authors, as required by the FGPS.

The first chapter provides a description of the different categories of antineoplastic therapies and considerations in treatment selection. Chapter 2 presents a general overview of the current knowledge on the pathophysiology of drug-induced cardiotoxicity in breast cancer. The third chapter consists of a manuscript summarizing the known effects of estrogen and estrogen-targeted therapies (ETs) on the cardiovascular system. A nested case-control study investigating the cardiovascular risks associated with ETs forms the basis of the manuscript found in Chapter 4. Building on this risk assessment, Chapter 5 is dedicated to the pattern of use of these antineoplastic drugs to determine if off-label use is based on credible evidence to avoid unnecessary hazardous side effects associated with these therapies. The last Chapter is a general discussion of these findings and their

relevance with regards to the treatment choice as well as the monitoring, prevention and management of cardiotoxicity in breast cancer patients.

Chapter 1

1. Breast Cancer Incidence and Treatment

Breast cancer is the most common site of malignant neoplasm in North America and the second leading cause of cancer death among women, after lung cancer (1) (2). In 2010, 206,966 American women were diagnosed with breast cancer and 40,996 succumbed to the disease (2). Early detection through regular mammography screening and improvement in treatment approaches have considerably helped reduce the number of breast cancer fatalities (1). Although nowadays standard treatments still include conventional modalities such as surgery, radiotherapy and chemotherapeutic agents, the discovery of distinct molecular characteristics of breast tumours has opened a new era of "smart" drugs with promising rates of breast cancer response. Cytotoxic antineoplastic drugs have been part of standard regimen to systemically treat various cancers for several decades. First used as chemical warfare agents during the World War I, physicians discovered that cytotoxic agents such mustard gas could damage rapidly growing cells and started to inject the drug intravenously to treat advanced lymphomas in the 1940s (3). Nowadays, hundreds of agents are used either alone or in combination to treat specific forms of cancer based on

their mechanism of action and side effects. A summary of the drugs approved by the FDA before June 30, 2013 is listed in **Table *1***.

Table 1: Categories and subcategories of antineoplastic drugs approved by the FDA before June 30, 2013

Categories	Subcategories	Drugs
Alkylating agents	Classical agents (nitrogen mustards, nitrosoureas and alkyl sulfonates)	Bendamustine, Busulfan, Carmustine, Chlorambucil, Cyclophosphamide, Ifosfamide, Lomustine, Mechlorethamine, Melphalan, Streptozocin, Uracil mustard
	Alkylating-like (Platinum)	Carbplatin, Cisplatin, Oxaliplatin
	Non-classical	Dacarbazine, Procarbazine, Thiotepa, Temozolomide
Anti-metabolites	Purine analogs	Cladribine, Clofarabine, Fludarabine, Mercaptopurine, Nelarabine, Pentostatin, Thioguanine
	Pyrimidine analogs	Azacitidine, Capecitabine, Cytarabine, Decitabine, Floxuridine, Fluorouracil, Gemcitabine, Liposomal cytarabine
	Antifolates	Methotrexate, Pemetrexed, Pralatrexate
	Others	Asparaginase, Hydroxyurea, Pegaspargase
Anti-tumor antibiotics	Anthracyclines	Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Liposomal daunorubicin, Liposomal doxorubicin, Valrubicin
	Others	Bleomycin, Mitomycin, Dactinomycin
Anti-mitotic agents	Vinca alkaloids	Vinblastine, Vincristine, Vinorelbine
	Taxanes	Cabazitaxel, Docetaxel, Liposomal paclitaxel, Paclitaxel
	Others	Eribulin mesylate, Estramustine, Ixabepilone
Hormone thrapies	Gonadotropin-releasing hormone agonists	Buserelin, Degarelix, Goserelin, Histrelin, Leuprolide, Triptorelin
	Anti-androgens	Bicalutamide, Enzalutamide, Flutamide, Nilutamide
	Others	Abiraterone, Fluoxymestrone
Immunotherapies	Monoclonal antibodies	Alemtuzumab, Bevacizumab, Brentuximab vedotin, Cetuximab. Gentuzumab ozogamicin, Ibritumomab, Ipilimumab, Ofatumumab, Panitumumab, Pertuzumab, Rituximab, Tositumomab, Trastuzumab
	IL-2 agents	Aldesleukin, Denileukin diftitox
	Immune modulators	BCG, Imiquimod, Interferon alfa-2a, Lenalidomide, Thalidomide
Small molecule inhibitors	HER family	Erlotinib, Gefinitib, Lapatinib
	Others	Aflibercept, Bortezomib, Bosutinib, Cabozantinib, Carfilzomib, Dasatinib, Everolimus, Imatinib, Nilotinib, Pazopanib, Ponatinib, Regorafenib, Romidepsin, Sorafenib, Sunitinib, Temsirolimus, Vemurafenib, Vismodegib, Vorinostat
Topoisomerase inhibitors	Type I	Topotecan, Irinotecan
	Type II	Etoposide, Mitoxantrone, Teniposide

1.1 Alkylating agents

Alkylating agents are used in a wide variety of cancer types including leukemia (4), lymphoma (5), multiple myeloma (6), sarcoma (7), and Hodgkin disease (8), as well as cancers of the breast (9), brain (10), lung (11), testicle (12), pancreas (13) (14) and ovary (15). They are highly reactive moieties that prevent cancer cells from reproducing through direct DNA damage by binding covalently to electron-rich nucleophilic positions on molecules such as DNA, RNA and proteins (16). The primary alkylating site for DNA is at the N7 position of guanine, although other interactions can occur (17) (18) (19). Other alkylation sites include positions N1 and O6 of guanine, N1, N3 and N7 of adenine position N3 of cytosine and position O4 of thymidine (20). Crosslinks with a single or both DNA strands prevent DNA replication and lead to double-strand breaks or single-strand gaps, leading to chromosomal aberration, breakage and apoptosis (16). These agents can also react with carboxyl, amino, hydroxyl, sulfhydryl and phosphate groups of other cellular components (21). Their effect is cell cycle-independent but dose-dependent (22). Alkylating agents are classified, based on their molecular structures, potency, toxicity and disease specificity, as: classical, alkylating-like platinum based and non-classical agents.

1.1.1 Classical alkylating agents

The two subtypes of classical alkylating agents are the nitrogen mustards and nitroureas. Nitrogen mustards are the oldest group of chemotherapeutic agents and alkylating agents in use today (3). They create interstrand DNA crosslinks which force the cell to undergo apoptosis (23). Chemotherapeutic agents derived from nitrogen mustard include bendamustine, busulfan, chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine, melphalan, and uramustine. Nitrosourea are alkylating agents that include a nitroso group and urea which decompose in aqueous solutions to result in isocyanate group and chloroethyl carbonium ion which reacts with DNA to form a mono and subsequently a bi-functional DNA crosslink (24). Although their mechanism of action is similar to nitrogen mustards, these agents are able to cross the blood-brain barrier due their lipophilic nature, making them useful in the treatment of brain tumors (25). Nitrosourea compounds currently available in the United States (US) for cancer treatment include carmustine, lomustine and streptozocin. Of the classical alkylating agents, only cyclophosphamide is indicated by the Food and Drug Administration (FDA) for breast cancer treatment. This drug is usually used in combination with other chemotherapeutic agents in this patient population (26).

1.1.2 Alkylating-like platinum-based agents

Alkylating-like platinum-based agents act in a similar fashion to classical agents despite the fact they do not have an alkyl group. Carboplatin, cisplatin and oxaliplatin are the main coordination complexes of platinum in this alkylating agent subcategory but none of them have been approved as breast cancer treatment. They require intracellular activation to reach cytotoxic efficacy (27) (28). They have the advantage of causing less long-term bone marrow damage, reducing the risk of leukemia following treatment when compared to other alkylating agents but have been associated with significant peripheral neuropathies (29).

1.1.3 Non-classical alkylating agents

No consensus exists on agents which should be included in this category. It includes various pro-drugs which must be oxidized or activated to form a cytotoxic moiety. Certain sources will explicitly distinguish tetrazines (dacarbazine, mitozolomide, temozolomide) and aziridines (thiotepa) from the non-classical category based on their distinctive reactive moieties (30). Procarbazine is pro-drug indicated for hodgkin and non-hodgkin lymphomas which leads to alkylating species and can also be categorised as a non-classical agent (31). Only thiotepa has obtained FDA-approval for breast cancer.

1.2 Antimetabolites

Antimetabolites structurally resemble nucleosides and impede RNA and DNA synthesis through incorporation into DNA and RNA at the S-phase of the cell cycle (32). These aberrant nucleoside analogs cause strand breaks or premature chain termination in a scheduled rather than dose-dependent fashion (33). Drugs in this category can also exert their effect by blocking enzymes required in DNA synthesis which leads to the prevention of mitosis (34). Antimetabolites can be subcategorised as anti-pyrimidines, anti-purines and anti-folates based on their mechanism of action.

1.2.1 Anti-pyrimidine

Anti-pyrimidines, such as fluoropyrimidines (5-fluorouracil, capecitabine, floxuridine) and deoxynucleoside analogues (azacitidine, clofarabine, cytarabine, liposomal cytarabine, decitabine, gemcitabine), are metabolised and misincorporated into RNA as cytosine and thymine analogs which interferes with DNA synthesis. Metabolites of fluoropyrimidines can also covalently bind to thymidylate synthase resulting in the inhibition of *de novo* synthesis of thymidine from deoxyuridine monophosphate (35). Antipyrimidines have been employed to treat a variety of neoplastic conditions, but only 5-

fluorouracil, capecitabine and gemcitabine are formally indicated for the treatment of breast cancer in the US.

1.2.2 Anti-purines

Antagonists of adenine and guanine are also used clinically to inhibit cancer cell proliferation. None are approved by the US FDA as breast cancer therapies, but they are routinely prescribed in oncology settings, especially in cases of lymphoproliferative diseases (36) (37) and leukemias (38) (39). Available agents include cladribine, fludarabine, mercaptopurine, nelarabine, pentostatin and thioguanine.

1.2.3 Anti-folates

Structurally related to folic acid, these drugs inhibit the regeneration of oxidized folates (tetrahydrofolates from dihydrofolates) which are required for purine synthesis and cell division (40). Methotrexate exerts its effect through inhibition of dihydrofolate reductase (DHFR) while pemetrexed can, in addition to DHFR, inhibit enzymes thymidylate synthase, aminoimidazole carboxamide ribonucleotide formyltransferase and glycinamide

ribunucleotide formyltransferase (41). In 2009, the FDA approved pralatrexate as another folate analog metabolic inhibitor for the treatment of relapsed or refractory peripheral T-cell lymphoma. This latest DHFR inhibitor is also a competitive inhibitor for polyglutamylation by folylpolyglutamyl synthase resulting in the depletion of thymidine and the synthesis of other molecule dependent on single carbon transfer (42). Methotrexate is the only folate antagonist with FDA-approval for breast cancer and is often used in combination with cyclophosphamide and 5-Fluorouracil (CMF) in that setting (43).

1.3 Cytotoxic Antibiotics

This category includes a wide variety of drugs with miscellaneous mechanisms of action such as DNA intercalation (44) (45), alteration of membrane fluidity and ion transport (46) (47), initiation of DNA cleavage by topoisomerase II (48), as well as the generation of semiquinone free radical (49) (50). They have clinical application at all phases of the cell cycle in treatment of hematologic cancers (51), sarcomas (52) and carcinomas; including carcinomas of the breast (53) (54). Anthracyclines were originally derived from *Streptomyces peucetius* and include daunorubicin, doxorubicin, epirubicin, idarubicin and valrubicin (55). More recently, liposomal formulations of daunorubicin and doxorubicin have reached the market. These new formulations are thought to enhance therapeutic ratio and reduce end-organ exposure and cardiotoxicity (56). Dactinomycin, bleomycin and

mitomycin are other cytotoxic antibiotics which are clinically available for the treatment of various malignancies. Dactinomycin inhibit DNA-dependent RNA synthesis through intercalation between guanine-cytosine pairs (57) (58) whereas bleomycin arrests cell division in G2-phase via the production of single and double strand breaks and free radical formation (59). It should be noted that although plicamycin was approved by the FDA in 1970, this cytotoxic antibiotic was discontinued from the market in 2000 and, is, therefore no longer available to prescribing physicians. Although cardiotoxicity considerably limits their usefulness, doxorubicin and epirubicin are recommended as first line agents for recurrent and metastatic breast cancer in several practice guidelines (60) (61).

1.4 Anti-mitotic agents

Nuclear division is a complex and highly regulated process. Segregation of chromosomes and mitosis is facilitated by mitotic spindle, a structure formed in part of kinetochore microtubules, polar microtubules and astral microtubules (62). Anti-mitotic agents interfere with cell division by affecting the dynamic structure of microtubules (63). Vinca alkaloids and taxanes are anti-mitotic agents which disrupt microtubule function in an opposite fashion and are used to treat many types of cancer including myelomas, leukemias, lymphomas, and carcinomas of the breast, prostate and lung (64).

1.4.1 Vinca Alkaloids

Vinca alkaloids agents are derived from *Catharanthus roseus* and bind to specific sites on tubulin dimers, inhibiting their assembly into microtubules (65). Their action is cell cycle-dependent as the binding to molecules occurs in the S-phase which prevents the formation of microtubules required for the M-phase (66). Vinblastine and vincristine are naturally occurring chemicals while vinorelbine and investigational agent vindesine are produced semi-synthetically. Although none have received FDA approval for treatment of breast carcinomas, several publications report their use in this clinical setting (67) (68) (69) (70).

1.4.2 Taxanes

Taxanes inhibit cell proliferation through microtubule depolymerisation which interferes with chromosome segregation and leads to mitotic arrest (71). Paclitaxel is a natural taxane extracted from the *Tavus brevifolia* Pacific Yew tree whereas docetaxel and cabazitaxel are semi-synthetic products. To overcome water solubility issues, an albumin-bound formulation of paclitaxel was approved by the FDA in 2005 (72). Paclitaxel and cabazitaxel exert their inhibitory functions at the boundary of the G2-S phases of the cell cycle (73) in contrast to docetaxel which affects the S-phase (74). All taxanes except cabazitaxel are indicated for the treatment of metastatic breast cancer.

1.5 Topoisomerase inhibitors

Topoisomerases control the three-dimensional conformation of DNA by catalyzing the reactions required to unwind DNA supercoils and allow for replication and transcription to ensue. These enzymes cleave and rejoin the phosphodiester backbone of DNA to reduce tension in the structure (75). Inhibitors are classified according to their target enzyme as topoisomerase I (TopI1) and topoisomerase II inhibitors (TopI2).

1.5.1 Topoisomerase I inhibitors (TopI1)

Type I topoisomerases preferentially bind to double-stranded DNA and generate single-strand breaks allowing rotation of the cleaved strand through the nick to release torsion stress (76). These monomeric proteins subsequently religate the cleaved strand to restore intact DNA duplex. Cleavage complexes formed of DNA and topoisomerase are generally transient and found in minute amounts, but topoisomerases have been found to be overexpressed in a variety of tumor types (77) (78) (79). TopI1 stabilize these complexes, hinder DNA religation which leads to DNA strand breaks and cell death (80). Two camptothecins derivatives have been approved as TopI1 by the FDA. Topotecan and irinotecan have been introduced into clinical practice for the treatment of ovarian (81) and lung cancer (82), and colon cancer (83), respectively. Novel TopI1 which are not derived

from the Chinese ornamental tree *Camptoteca acuminate* are presently under evaluation in clinical trial settings (22).

1.5.2 Topoisomerase II inhibitors (TopI2)

Unlike type I, type II topoisomerases cleave both DNA strands simultaneously in an ATP-dependent mechanism, relieving the DNA helix of 2 units of linking number (84). TopI2 convert cleavable complexes into stable protein-associated breaks in the genome of treated cells (85). Inhibitors used in cancer clinics include members of the epipodophyllotoxin family etoposide and teniposide, as well as the anthracenadione mitoxantrone. None have obtained FDA-approval for a breast cancer indication.

1.6 Immunotherapy

These agents use natural defences of cancer patients to recognize and target cancer cells. Immunotherapy can actively stimulate the patient's immune system to mount a response or can rely on passive immunity, using engineered immune components. This

therapeutic approach is still fairly new and is comprised of monoclonal antibody therapies, immunomodulating drugs and cancer vaccines.

1.6.1 Monoclonal Antibodies

Considerable efforts have been deployed to develop targeted therapies against oncogenes driving tumorigenesis. Monoclonal antibodies can target cancer cell for destruction or prevent tumor growth by blocking the activity of growth factors. The specificity of their inhibitory activity is dependent on the presence of tumor-specific antigen which permits discrimination between normal and cancerous cells. This therapeutic approach has been employed in the treatment of a variety of malignancies including breast carcinomas. Trastuzumab is the hallmark of immunotherapy for breast cancer treatment and was the second monoclonal antibody approved by the FDA as a cancer therapy after rituximab. Amplification of the ERBB2 gene occurs in about 15 to 30% of breast cancer cases and is associated with an adverse prognosis and tumor aggressiveness (86). Trastuzumab is a humanized monoclonal antibody developed to recognise the extracellular portion of the growth factor receptor ErbB-2 also called Her-2 (87). This biological agent has become the gold standard in treatment of ERBB2 amplified breast tumors (60). However, clinical trials have demonstrated that its antitumor effect is short-lived with progression after 9.1 months of treatment on average (88) (89). Another monoclonal antibody was

recently approved by the FDA to target ErbB-2 signalling in breast tumors. Pertuzumab prevents the heterodimerization of ErbB-2 with its co-receptors (90). Newer approaches have been investigated such as radioimmunotherapy which uses antibodies conjugated to radioisotopes to deliver radioactivity specifically at the site of radio-sensitive tumors (91). Monoclonal antibody therapy has also been used as a vehicle to deliver cytotoxic drugs at the tumor site. Kadcyla (trastuzumab emtansine) was approved by the FDA in 2013 to target anti-mitotic agent mertansine directly to Her-2 positive breast tumor site. Trastuzumab targets Her-2, a potent oncogene known to be amplified in a variety of tumors (92) (93) (94), but other monoclonal antibodies have been developed against diverse antigens driving tumor progression. A list of FDA-approved agents can be found in **Table *2***. However, it should be noted that only trastuzumab and pertuzumab are indicated for the treatment of breast cancer. Although bevacizumab received market approval for this indication in early 2008, the FDA revoked this decision in November 2011 after revision of its risk/benefit analysis (95).

Table 2: US Food and Drug Administration (FDA) – approved monoclonal antibodies as cancer therapies (2013)

Drug	Target	Indication
Alemtuzumab	CD52	Chronic lymphocytic leukemia
Bevacizumab	VEGF	Metastatic colorectal carcinoma, Non-squamous NCLC, Glioblastoma, Metastatic renal cell carcinoma[1]
Brentuximab vedotin	CD30	Hodgkin lymphoma, anaplastic large cell lymphoma
Cetuximab	EGFR	Head and neck cancer, colorectal cancer
Gemtuzumab ozogamicin	CD33	Acute myeloid leukemia
Ibritumomab tiuxetan	CD20	Non-Hodgkin's lymphoma
Ipilimumab	CTLA-4	Melanoma
Ofatumumab	CD20	Chronic lymphocytic leukemia
Panitumumab	EGFR	Metastatic colorectal carcinoma
Pertuzumab	Her-2	Her-2 positive breast cancer
Rituximab	CD20	Non-Hodgkin's lymphoma, Chronic Lymphocytic Leukemia, Rheumatoid arthritis, Granulomatosis with polyangiitis, Microscopic polyangiitis
Tositumomab	CD20	Non-Hodgkin's lymphoma
Trastuzumab emtansine	Her-2	Her-2 positive breast cancer
Trastuzumab	Her-2	Her-2 positive breast cancer, metastatic gastric or gastroesophageal junction carcinoma

CD20: Cluster of differentiation 20
CD30: Cluster of differentiation 30
CD33: Cluster of differentiation 33
CD52: Cluster of differentiation 52
CTLA-4: Cytotoxic T-lymphocyte antigen 4
EGFR: Epidermal Growth Factor Receptor
Her-2: Human Epidermal Growth Factor Receptor 2
NSCLC: Non-small cell lung carcinoma
VEGF: Vascular endothelial growth factor
[1]FDA revoked breast cancer as an indication for bevacizumab on November 18, 2011

1.6.2 Immunomodulators

Several cytokines (INF-α, aldesleukin and denileukin diftitox) have been approved as immunotherapies for clinical use, but none thus far for the treatment of breast cancer. Although they may have multiple mechanisms of action, thalidomide and its analogs can also alter the expression of inflammatory cytokines (96). Analogs lenalidomide and pomalidomide are significantly more potent than thalidomide in anti-inflammatory properties (97). Other molecules such as imiquimod are used in skin cancer and metastases to activate the innate arm of the immune system through the toll-like receptor-7 (98) (99).

1.6.3 Cancer Vaccines

Traditional vaccines to prophylactically prevent the development of infections have been around since Edward Jenner induced immunity to smallpox through cowpox vaccination. Immunization to the human papilloma or hepatitis B viruses has helped reduce the incidence of cervical (100) and liver cancers (101), respectively. However, only limited success was obtained in the active immunization and treatment of active cancers. Provenge, designed to treat prostate cancer, is the only therapeutic vaccine to date to have obtained FDA approval for generating an immune response and increasing the survival of cancer patients (102). This breakthrough has raised awareness and other investigational

vaccines are being tested in clinical trials for their capacity to mount a tumor-specific immune response. Phase III clinical studies are currently ongoing to test the safety and efficacy of a vaccine recognizing the E75 peptide of ErbB-2 in the prevention of breast cancer recurrence (103).

1.7 Small-molecule inhibitors

Small molecule inhibitors specifically target effector proteins that are needed for cancer development, maintenance, invasion or proliferation. They attenuate oncogenic signals through inhibition of key molecules such as kinases, phosphatases and deacetylase which can be growth factors, growth factor receptors, signal transducers, regulators of protein stability or translation, cell cycle modulators, and angiogenesis factors. To date, 22 of such inhibitors have received FDA approval as cancer treatments (**Table *3***) but only two of them are indicated for breast cancer. Lapatinib directly targets the tyrosine kinase domain of both the epidermal growth factor receptor (EGFR) and Her-2 to inhibit receptor autophosphorylation upon ligand binding which consequently prevents further downstream signalling (104). It is indicated for the treatment of patients with advanced or metastatic Her-2 positive breast cancer with prior exposure to anthracycline, taxane and trastuzumab, or in combination with letrozole for the treatment of post-menopausal women with hormone-dependent, Her-2 positive metastatic breast cancer (105). On July

20th, 2012, everolimus was approved by the FDA for the treatment of post-menopausal women with advanced hormone receptor positive, Her-2 negative breast cancer in combination with exemestane, after failure of treatment with a non-steroidal aromatase inhibitor (anatrozole or letrozole) (106). Other drug candidates are in the pipeline for breast cancer treatment. These investigational agents include inhibitors of mammalian target of rapamycin (mTOR) (107), poly ADP ribose polymerase (PARP) (108), phosphoinositide 3-kinase (PI3K) (109), gamma secretase/Notch signalling (110), cyclin-dependent kinase, protein kinase B (AKT) (111), and insulin growth factor receptor (IGFR) (112). Small molecule inhibitors are the most intensively pursued classes of cancer drug targets with 13 new molecular entities approved for the American market in 2012-2013.

Table 3: US Food and Drug Administration (FDA) - approved small molecule inhibitors as cancer therapies (2013)

Drug	Target	Indication
Aflibercept	VEGF	Metastatic colorectal cancer
Bortezomib	Proteasome	Multiple myeloma, Mantel cell lymphoma
Bosutinib	Bcr-Abl	Ph+ Chronic myeloid leukemia
Carfilzomib	Proteasome	Multiple myeloma
Cabozantinib	c-Met, VEGFR2	Metastatic medullary thyroid cancer
Dasatinib	Bcr-Abl	Ph+ Chronic myeloid leukemia
Erlotinib	EGFR	NSCLC, Metastatic pancreatic cancer
Everolimus	mTOR	Hormone(+). Her-2 (-) breast cancer, neuroendocrine tumor of pancreatic origin, renal cell carcinoma, renal angiomyolipoma and TSC, subependymal giant cell
Gefitinib	EGFR	NSCLC
Imatinib	Bcr-Abl, KIT, PDGF, SCF	Ph(+) Chronic myeloid leukemia, KIT(+) malignant GIST
Lapatinib	Her-2	Her-2(+) breast cancer
Nilotinib	Bcr-Abl	Ph(+) Chronic myeloid leukemia
Pazopanib	VEGFR, PDGFR, FGFR, KIT, Itk, Lck, c-Fms	Renal cell carcinoma, soft tissue sarcoma
Ponatinib	Bcr-Abl	Ph(+) Chronic myeloid leukemia
Regorafenib	RET, VEGFR, KIT, PDGFR, FGFR, TIE2, DDR2, TrkA, EphA2, RAF-1, BRAF, SAPK2 PTK5, Abl	Metastatic colorectal cancer, GIST
Romidepsin	HDAC	CTCL, PTCL
Sorafenib	RAF-1, BRAF, KIT, FLT3, RET, RET/PTC, VEGFR, PDGFR	Hepatocellular carcinoma, Thyroid carcinoma
Sunitinib	PDGFR, VEGFR, KIT, FLT3, CSF-1R, RET	GIST, Renal cell carcinoma, Pancreatic neuroendocrine tumor
Temsirolimus	mTOR	Renal cell carcinoma
Vemurafenib	BRAF	BRAF V600E(+) Melanoma
Vismodebig	SMO	Basal cell carcinoma
Vorinostat	HDAC	CTCL

Abl: Abelson murine leukemia viral oncogene homolog 1
Bcr: Breakpoint cluster region protein
BRAF: v-RAF murine sarcoma viral oncogene
c-Fms: Transmembrane glycoprotein receptor tyrosine kinase
c-MET: Hepatocyte growth factor receptor
CTCL: Cutaneous T-cell lymphoma
DDR2: Discordin domain-containing receptor 2
EGFR: Epidermal Growth Factor Receptor
EPH2A: Ephrin receptor A2
FGFR: Fibroblast growth factor receptor (1 and 3)
FLT-3: Fms-like tyrosine kinase-3
GIST: Gastrointestinal stromal tumors
HDAC: Histone deacetylase
Her-2: Human Epidermal Growth Factor Receptor 2
Itk: Interleukin-2 receptor inducible T-cell kinase
KIT: Mast/stem cell growth factor receptor/cluster of differentiation 117
Lck: Leukocyte-specific protein tyrosine kinase
mTOR: Mammalian target of rapamycin
NSCLC: Non-small cell lung carcinoma
PH: Philadelphia chromosome
PDGFR: platelet-derived growth factor receptor (α and β)
PTC: Papillary thyroid cancer
PTCL: Peripheral T-cell lymphoma
PTK5: Fyn-related kinase-5
RAF-1: Proto-oncogene serine/threonine-protein kinase
RET: Glial cell-line derived neurotrophic factor receptor
SAPK2: Stress-activated protein kinase 2
SCF: Stem cell factor
SMO: Smoothened receptor
TIE2: Endothelial-specific receptor tyrosine kinase 2
TrkA: High affinity nerve growth factor receptor
TSC: Tuberous sclerosis complex
VEGF: Vascular endothelial growth factor
VEGFR: Vascular endothelial growth factor receptor (1, 2 and 3)

1.8 Hormonal agents

The endocrine system can be manipulated to slow the growth of hormone-dependent breast, endometrial and prostate cancers. This therapeutic approach relies on the administration of exogenous hormones to reduce the endocrine response or on the inhibition of hormone production. The major categories of hormonal agents include estrogen-targeted therapies (ETs), gonadotropin-releasing hormone (GnRH) analogs, and androgen agonists and antagonists.

1.8.1 Estrogen-targeted therapies (ETs)

Selective estrogen receptor modulators or down-regulators (SERM/DRs) and aromatase inhibitors (AI) are the gold standard in the treatment of estrogen-positive breast cancer. SERM/DRs are competitive antagonists of the estrogen receptor (ER) whereas AIs inhibit the conversion of androgens to estrogens (113). Selective estrogen receptor down-regulators (SERD) differ from modulators (SERM) in being pure antagonists of ER (114). SERM can antagonise the effect of estrogen in some tissues while displaying agonistic activity in others. This dual effect on the ER is thought to be responsible for the anti-proliferative effect of tamoxifen on breast cancer cells and increased risk in endometrial cancer observed following treatment (115). The selective estrogen receptor modulator and

down-regulators approved for breast cancer in the US include tamoxifen, toremifene and fulvestrant, whereas anastrozole, letrole and exemestane are the third-generation of aromatase inhibitors approved for this indication.

1.8.2 Gonadotropin-releasing hormone (GnRH) agonists

These synthetic peptides are used to induce a chemical castration in patient with hormonally responsive tumors. Analogs of the neurohormone GnHR bind to their target receptor in an irreversible fashion which ultimately results in the down-regulation of GnRH receptors together with decreases in follicle-stimulating hormone (FSH) and luteinizing hormone (LH) secretion (116). Goserelin is the only GnRH agonist to be approved by the FDA to disrupt the endogenous hormonal feedback leading to the down-regulation of estrogen production in breast cancer (117). Although not formally approved for this indication, use of leuprolide in the context of breast carcinoma has been often reported (118) (119) (120).

1.8.3 Androgen agonists and antagonists

Drugs in this class bind to the androgen receptor to block the growth and survival of testosterone-dependent prostate cancer cells. Fluoxymesterone is the only steroid with androgenic properties to be indicated for breast cancer. This anabolic steroid is an agonist of the androgen receptor but may also exert its antineoplastic effect in breast cancer cells via antagonistic activity on the ER (121) (122).

1.9 Considerations in treatment selection

Prognosis and selection of a therapy may be influenced by a variety of clinical and pathological considerations. Therefore, a multifactorial approach must be taken in the assessment of the best therapeutic option. Studies have shown that age, stage of the disease, tumor molecular profiling, socioeconomic and sociodemographic characteristics, performance status of the patient and treatment safety profile all influence treatment decisions. The most common drug combinations used for the treatment of breast cancer are presented in **Table *4***

Table 4: Common drug combinations used in the treatment of breast cancer

Abbreviation	Drug combination
CAF	Cyclophosphamide, doxorubicin, 5-Fluorouracil
TAC	Docetaxel, Doxorubicin, Cyclophosphamide
TC	Docetaxel, Cyclophosphamide
TCH	Docetaxel, Carboplatin, Trastuzumab
AC +T	Doxorubicin, cyclophosphamide, followed by paclitaxel
FED+T (1)	5-Fluorouracil, Epirubicin, Cyclophosphamide, followed by docetaxel
FED+T (2)	5-Fluorouracil, Epirubicin, Cyclophosphamide, followed by paclitaxel
CMF	Cyclophosphamide, Methotrexate, 5-Fluorouracil
A+CMF	Doxorubicin, followed by Cyclophosphamide, Methotrexate, 5-Fluorourac
EC	Epirubicin, Cyclophosphamide
AC +T	Doxorubicin, Cyclophosphamide

1.9.1 Age and age-related status

Aging implies a reduction in life expectancy and tolerance to aggressive treatments (123) (124) (125). Advanced age is often associated with impairment of physiological functions leading to important pharmacokinetic and pharmacodynamic changes (126). Decreased tolerability and effectiveness of cyclophosphamide, methotreaxete and fluorouracil (CMF) treatment was reported in older patients enrolled in the International Breast Cancer Study Group (IBCSG) (127). In clinical decision making for elderly patients, short term risks associated with treatment must be balanced against potential survival gain; while taking into consideration that a nonlinear relationship exists between age and life-expectancy (128). Dose intensity reduction may be required in older patients due to physiological changes rendering the geriatric population more susceptible to

chemotherapy-induced toxicities (129). Menopause is an age-related status which affects the choice of adjuvant hormonal treatment in ER-positive breast cancer (130). Aromatase inhibitors are not routinely administered as a monotherapy in the pre-menopausal setting as the effect on estradiol levels and long-term outcome remain questionable and under investigation (131) (132).

1.9.2 Histological classification and stage of the disease

The histological grade of the primary tumor and stage of the disease will help formulate therapeutic decisions based on aggressiveness of disease and prognosis. Although 70-80% of breast cancer cases are infiltrating or invasive ductal cancer, treatment options will vary between histological types (133). For non-invasive conditions such as ductal carcinoma *in situ* (DCIS), surgery may be more appropriate than an aggressive chemotherapeutic approach (134). A complete histological classification of breast cancer can be found in **Table *5***. The American Joint Committee on Cancer (AJCC) established a staging system to classify cancer progression. The TNM Classification is based on the size or direct extent of the primary tumor, the degree of spread to regional lymph nodes and the

presence of distant metastasis (135). In addition to molecular markers, these properties provide insight on expected prognosis as well as treatment responses and decisions (136).

Table 5: Histological Classification of Breast Cancer

Types	Subtypes
Carcinoma	NOS
Ductal	Intraductal (*in situ*)
	Invasive with predominant intraductal component
	Invasive, NOS
	Comedo
	Inflammatory
	Medullary with lymphocytic infiltrate
	Mucinous (colloid)
	Papillary
	Scirrhous
	Tubular
	Other
Lobular	*In situ*
	Invasive with predominant *in situ* component
	Invasive
Nipple	Paget disease, NOS
	Paget disease with intraductal carcinoma
	Paget disease with invasive ductal carcinoma
Other	Undifferentiated carcinoma
Atypical	Phyllodes tumor
	Angiosarcoma
	Primary lymphoma

NOS: Not otherwise specified

Ref: National Cancer Institute-Breast Cancer Treatment (PDQ)

1.9.3 Molecular determinants

DNA genotyping and gene expression profiling has led to the identification of molecular determinants of chemosensitivity. Molecular profiling is now integrated into the characterization of breast tumors and treatment decisions. Four distinct breast cancer subtypes have been characterized (luminal A, luminal B, basal-like/triple-negative and Her2+) based on the expression of the ER, progesterone receptor (PR), Her-2+ and antigen KI67 (**Table *6***) (137) (138). As previously described in section 1.8, hormonal therapies such as SERMs and AIs are at the forefront of estrogen-responsive breast cancer treatment. Tumors overexpressing the growth factor receptor Her-2 are likely to benefit from trastuzumab, pertuzumab or lapatinib therapy.

Table 6: Breast Cancer Subtypes based on Molecular Profiling

Subtype	Most common expression profile	Prevalence
Luminal A	ER+ and/or PR+, Her2-, low Ki67	40%
Luminal B	ER+ and/or PR+, Her2+ (or Her2- and high Ki67)	20%
Basal-like/Tripe negative	ER-, PR-, Her2-	15-20%
Her2	ER-, PR-, Her2+	10-15%

1.9.4 Socioeconomic and sociodemographic characteristics

Ethnic variations in the stage of breast cancer at diagnosis (139) (140) (141) (142) and selection of therapeutic options (143) (144) have led to investigations on the potential effect of sociodemographic factors in treatment decisions. Drug coverage plans have been reported as predictors of treatment selection (145) (146) and have led to disparity in access to drugs (147). Furthermore, marital status has been associated with selection of high risk curative options in various cancer types as opposed to less aggressive approaches (148) (149). Although physicians strive to determine the most clinically appropriate treatment, the selected options must account for patient preferences and concerns about body image (150). Patients will tend to favor a therapeutic modality which causes minimal disruption in their quality of life and independence (151), but are willing to accept risk of major toxicity for minimal increase in survival (152). Proximity of a treatment centre to patient's residence is a geographic consideration that can have a significant impact on treatment access (153) (154) (155) (156). Adoption of innovative therapeutic approaches appears to vary across treatment centres depending on caseload and participation in multicentre clinical trials (157). The hospital size also affects treatment decisions in women diagnosed with early breast cancer (158).

1.9.5 Performance status

Although efficacy is a clear driving force in treatment selection, the patient's overall health status is also an important factor for treatment algorithm. The Eastern Cooperative Oncology Group (ECOG) system has been used to score patient's performance status to determine prognosis and inform therapeutic decisions (**Table** *7*) (159). Cancer patients with a good performance status are more likely to derive survival benefits from aggressive combination regimen than those with a more precarious status (160). These patients are more likely to experience severe drug related toxicity which may result in dose reduction or early treatment termination (161).

Table 7: ECOG Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

1.9.6 Treatment safety profile

Although there is no clear benchmark for what constitutes an acceptable level of risk, treatment decisions are based on risk/benefit assessments (162). These evaluations are based on the safety and efficacy data derived from clinical trials, observational studies and experience. Safety concerns may even arise from preclinical studies or theoretical risks based on the drug's mechanism of action. Synergic effects of polypharmacy should be considered not only for its potential added benefits, but also in terms of toxicity. Paclitaxel and trastuzumab were shown to aggravate anthracycline-induced cardiotoxicity in breast cancer patients (163). Cardiotoxicity of anti-cancer agents have led to significant challenges in treatment decisions and clinical complications in treated patients.

Chapter 2

2. Breast cancer and cardiovascular diseases

Cancer survivors are at greater risk of cardiovascular diseases in comparison to the general population since cytotoxic therapies and biologic response modifiers, including classical chemotherapies and targeted agents such as monoclonal antibodies and small molecule inhibitors can affect cardiovascular health (164). Furthermore, cardiovascular disorders are among the most prominent comorbidities in breast cancer patients (165). In the early days of cancer treatment, the cardiotoxicity of therapies was less evident due to the limited life expectancy of patients with metastatic disease. Early diagnosis and the development of innovative therapies targeting distinct molecular determinants of tumor progression have led to significant improvement in the prognosis of breast cancer (166). This favorable trend in survival has resulted in an increased awareness of cardiovascular risks associated with anticancer drugs. This consideration is particularly relevant in breast cancer survivors because the affected population is generally older and more prone to underlying cardiovascular diseases (167).

Despite being the leading cause of death among American women with approximately 500,000 deaths annually (168), the risk of cardiovascular diseases is often

underestimated in female populations and is thought to be even further underestimated for breast cancer survivors because of a focus on breast cancer recurrence (169) (170). In 2007, 1 in 4.5 female died of cancer, whereas 1 in 2.9 died of cardiovascular diseases (171). The prognosis of heart failure and stroke has sometimes been reported to be worse than that of cancer (167) (172) (173) (174). Cardiotoxicity can become the dose limiting factor in cancer treatment, and hence response to therapy (175). Certain drug combinations may be inappropriate in patients with poor cardiovascular health due to their synergistic damaging effects on the myocardium and vasculature. Side effects on the myocardium may cause irreversible damage leading to severe, long-term morbidity in breast cancer survivors (176). Different factors, intrinsic to the mechanism of action of the antineoplastic drugs or the method of administration, may modulate the cardiotoxicity profile of certain classes of therapy or certain agents within a particular drug class. Specific patient characteristics and comorbidities also factor in the variability of the cardiovascular safety profile of these therapies. Several strategies have been employed in an attempt to predict and minimize the risks, but ideal monitoring techniques and prophylaxis have yet to be determined.

2.1 Pathophysiology of drug-induced cardiotoxicity

The term cardiotoxicity has been defined in general terms by the National Cancer Institute as “toxicity that affects the heart”. However, the clinical manifestation of

cardiotoxicity can take various forms ranging from acutely induced electrophysiological and hemodynamic changes to variations in coronary vasomotion or heart muscle contractility leading to potentially fatal heart failure (177). In order to be considered drug-related, the spontaneous occurrence of a new cardiovascular effect must occur in temporal association with the start of therapy or new dosage. Certain drugs, or their metabolites, can cause transient and fully reversible disturbances, whereas others can lead to chronic irreversible dysfunctions. The National Cancer Institute in the United States has developed a common terminology grading criteria for adverse events associated with therapy (178). Different cardiovascular outcomes are graded according to severity on a scale of 1 to 5, the latter representing death. The pathophysiology of adverse cardiovascular effects is heterogeneous. The combination of different types of therapies may hinder the identification of underlying mechanisms of toxicity. The spectrum of systemic and localised cardiotoxic effects includes direct myocardial injuries, rhythm disturbances, hemodynamic changes, thrombotic events, atherosclerosis, ischemia, coronary heart diseases, myocardial infarction, left ventricular dysfunction and heart failure.

2.1.1 Direct myocardial injury

Pharmacological agents may exert their cardiotoxic effects by interacting directly with cardiomyocytes. This mechanism of cardiotoxicity is not thought to play a significant role in the cardiac effects of endocrine therapies, but was shown to be responsible for

significant damage following treatment with other breast cancer therapies (179) (180). The morphologic reaction is usually dose and time dependent. It can often be detected in laboratory animals contingent upon the accurate characterization of the pharmacokinetics, more specifically, the drug metabolism. Consequently, acute and repeated toxicity assessment in at least two animal species is a pre-clinical regulatory requirement in drug development for several jurisdictions (181) (182) (183). Structural-functional correlations can be drawn from localized lesions disturbing the homeostasis of the cardiac system. Cell damage or necrosis can affect various cardiac muscle subcellular organelles including the mitochondria, myofibril, sarcoplasmic reticulum, sarcolemma, nucleus, nucleolus, lysosome and residual bodies. The degenerative lesions can lead to changes in plasma membrane permeability, modification of the cell's contractile capabilities and oxidative stress.

2.1.2 Cellular contractility

Response to injury will depend on the tissue component affected by the cardiotoxic agents. Cardiac muscle cells are the most commonly targeted tissue component in drug-induced myocardial damage and have limited response capability to injury. Reversible disturbances leading to hypertrophy of cardiac cells can have a significant impact on the overall cardiac function. Drug-induced myocardial damage generally consists of multifocal areas of degeneration, inflammation, necrosis, or fibrosis. Regeneration in the context of

cardiac function is fairly limited in comparison to other organs and usually results in necrosis followed by fibrosis. The death of cardiomyocytes will often lead to the hypertrophy of remaining cells and extensive fibrosis from the excess extracellular matrix accumulation. Hypertrophic cardiomyopathies reduce the contractibility of muscle cells and result in myocardial disarray and disruption of the electrical function of the heart. Dilated cardiomyopathies are often seen in patients with prolonged tachycardia and breast cancer patients subjected to chemotherapy regimens, especially in those treated with anthracyclines and trastuzumab (179) (180) (184). The clinical course of hypertrophic cardiac disorders is variable, but patients may experience dyspnea, angina, palpitations, syncope and sudden cardiac death.

2.1.3 Oxidative stress

Certain pharmacologic agents can generate reactive oxygen species which, in excess, can lead to oxidative stress and oxidation of cellular structures such as proteins, lipids and DNA (185) (186) (187) (188) (189). Mammalian tissues express several oxidant enzymes to help protect against the damaging effect of reactive oxygen species, but in comparison, the heart was shown to present reduced levels of these enzymes including catalase, glutathione peroxidase and superoxide dismutase (190) (191). Cardiac myocytes are rich in mitochondria which contains enzymes able to mediate electron reduction

producing a high concentration of reactive oxygen species (192). Under oxidative stress conditions, cumulative mitochondrial DNA damage leads to irreversible mitochondrial dysfunction of the heart. The effect of oxidative damage is far greater on mitochondrial DNA than on nuclear DNA and the repair processes are much less efficient. Defective mitochondrial oxidative phosphorylation leads to the depletion of cellular ATP and cell necrosis (193) (194). Oxidative stress may also increase the risk of artheriosclerosis through the oxidative modification of low-density lipoproteins in the arterial wall by reactive oxygen species (195).

Although oxidative stress can be detected in various cardiovascular disorders, it could be the result of some secondary effect of the disease process and a direct causal relationship has yet to be fully established (196). Nonetheless, oxidative stress has been linked to atherosclerosis, hypertension, contractile dysfunctions and arrhythmias via an increase in Ca^{2+} into vascular myocytes. This overload in intracellular Ca^{2+} may also be responsible for the oxidative stress-dependent transition of cardiac hypertrophy to heart failure (197). The formation of reactive oxygen species by various pharmacologic agents can lead to cardiomyocyte necrosis, collagen synthesis, and fibroblast proliferation which results in fibrosis and myocardial stiffness (198). Additional structural and functional deteriorations can ensue in the form of cardiac hypertrophy and ventricular remodelling (199) which cause diastolic dysfunction and reduced contractile capability. Ultimately, oxidative stress may lead to heart failure and sudden death.

Markers of constitutive oxidative stress have been reported in breast carcinomas samples (200) with a high prevalence of major oxidatively modified DNA products such as 8-Hydroxy-2'-deoxyguanosine up to ten times higher than in normal control samples (201). The inadequate tumor vasculature network and the infiltration of macrophage at the tumor site are both factors leading to persistent oxidative stress, but several chemotherapeutic agents can further add to the oxidative stress within the tumor and at distant sites (202). Doxorubicin, etoposide, Mitomycin C, cisplatin and radiotherapy have all shown superoxide generating capabilities and significant cardiovascular effects (203).

2.1.4 Rhythm disturbances

The prevalence of atrial fibrillation and rhythmic disturbances in breast cancer patients was reported to be twice as high as in controls of similar age (204). Pharmacological agents can directly contribute to cardiac arrhythmogenesis by affecting the heart's conduction system; or indirectly via modulation of the sympathetic or parasympathetic nervous system; or by causing physiological disturbances, such as electrolyte imbalance or hypotension. The type of arrhythmias induced by drugs can vary widely depending on the mechanism of cardiac toxicity. Serious rhythm disorders can arise from drug-induced alterations of ventricular depolarization and repolarization. There are two distinct categories of drug-induced ventricular arrhythmias: monomorphic ventricular

tachycardia and the polymorphic ventricular tachycardia, also known as torsades de pointes.

The mechanisms leading to drug-induced monomorphic ventricular tachycardia vary according to the causative agents, but many drugs modulate their cardiotoxic effect via a reduction in ventricular conduction velocity as a result of potent inhibition of myocardial sodium channels (205). Enhancement of arterial chemoreceptor and baroreceptor activity leading to increased sympathetic nervous system activity may result in this type of tachycardia (206). The clinical presentation consists of a series of consecutive ventricular premature repolarization and can be diagnosed by its typical misshapen QRS complexes with sinusoidal appearance on an electrocardiogram in combination with increased heart rate (>100bpm). While drug-induced monomorphic ventricular tachycardia can be terminated spontaneously, the effect can be sustained for more than 30 seconds and require intervention for termination. Symptoms are mostly related to heart rate and the resultant effect on cardiac output and blood pressure, including hypotension, palpitations, chest pain, syncopes and, in some cases, sudden death. The onset of drug-related monomorphic ventricular tachycardia is variable and dependent on plasma drug concentration and patient's susceptibility to cardiac rhythm disturbances. Although the arrhythmia can develop between a few minutes to several hours, the majority of cases occur within hours or days after therapy initiation. Many conditions must be considered in the differential diagnosis of drug-induced monomorphic tachycardia. Diagnosis is usually

based on the occurrence of new ventricular tachycardia in a patient with no prior history of this disorder or tachycardia with new morphology in a patient with history of non-drug-induced ventricular tachycardia. Incessant sinusoidal ventricular tachycardia can also be considered drug-induced, as this form of tachycardia has only been described in presence of drug therapy. Monomorphic ventricular tachycardia has been reported in breast cancer patients following treatment with anthracycline doxorubicin (207).

Polymorphic ventricular tachycardia is defined as a ventricular rhythm faster than 100 beats/min with frequent variation in the QRS axis (208) (209). In cases of torsades de pointes, these variations can take the form of cyclic sinusoidal alteration of the QRS complex which appears to twist around the isoelectric baseline which can be acquired or congenital (210) (211). Acquired torsades de pointes are primarily a result of drug therapy, hypokalemia or hypomagnesemia. The illusion of twisting of the QRS complex around the isoelectric baseline is a characteristic electrocardiogram presentation of this polymorphic ventricular tachycardia. Torsades de pointes are often associated with prolongation of the QT interval which occurs when the action potential of a large number of ventricular myocytes are extended. Action potential results from the coordinated function of various electrophysiological currents. Sodium and calcium inward ion channel activities are responsible for the action potential upstroke and depolarisation while outward potassium currents lead to myocyte repolarization and restoration of the negative myocardial intracellular polarity at rest (212) (213). QT prolongation occurs as a result of reduced

repolarizing currents and/or an increase in inward currents (214). Prolongation of ventricular repolarization, and its resulting action-potential duration lengthening, is the most common cause of drug-induced long QT syndrome. It is principally accomplished via inhibition of the rapidly activating delayed rectifier potassium channels (215) (216) (217) (218). Some drugs appear to prolong ventricular action potential through the activation of slow sodium current or increased inward calcium current (216) (218) (219).

The main symptoms associated with torsades de pointes and QT prolongation include seizure, chest pain, palpitations, syncope, and sudden death. The effect is usually short-lived, but most patients will experience rapid succession of multiple episodes which may ultimately degenerate to ventricular fibrillation and sudden death. The time from therapy initiation to development of torsades de pointes is variable, but tends to coincide with the time of peak in concentration of the causative agent. Induction time may be delayed for oral drugs and may be observed more than 30 days after therapy initiation. Drug-induced torsades de pointes appear to rarely occur in patients without additional risk factors (220). Prior conduction or structural abnormalities and use of concomitant medications known to cause rhythmic disturbances substantially increase the likelihood of tachycardia episodes (217) (218) (221). There appear to be a female predisposition to torsades de pointes (222) (223) (224) (225) (226). Although exact reasons remain elusive, difference in sex hormones have been suggested as potential risk modifiers (227). Decrease in the progesterone to estradiol ratio is thought to be arrhythmogenic; while testosterone

could have protective effect (228) (229). This arrhythmogenic effect is thought to be the result of the action of sex hormones on ion channel expression (230).

Several neoplastic agents have been shown to induce QT prolongation. The incidence of rhythmic disturbance can be as high as 10 to 30% in patients receiving anthracycline therapy (231) and combination with trastuzumab appears to potentiate the effect (232). The cardiotoxic effect of anthracycline doxorubicin can be reduced by using a liposomal formulation of the drug (233). The antimetabolite 5-fluorouracil (234) and anti-mitotic paclitaxel (235) (236) (237) can also induce electrocardiographic changes in breast cancer patients. The inherent arrhythmic properties of various chemotherapies are further complicated by combination regimen used to treat advanced disease. Since most therapies are used sequentially or in combination with other cytotoxic agents and many patients experience cardiovascular comorbidities prior to treatment, the actual cardiovascular risks associated with a certain therapy can be confounded or potentiated by concomitant medications and inherent risk factors.

2.1.5 Hemodynamic changes

Hypertension is the most frequent comorbidity reported in patients with malignancies (238) and was even suggested to directly affect the prognosis of this patient population (239). Anticancer medications have been associated with increased blood pressure (240). The most commonly reported mechanisms for chemotherapy-induced blood pressure elevation include endothelial dysfunction associated with reduced nitric oxide, increased vascular and renal endothelin production (241), vascular rarefaction (242), changes in vascular tone (238), upregulation of the renin-angiotensin-aldosterone system (243) (244), and impaired vasoconstriction (240). A significant dose-dependent increase in hypertension has been reported in 20% to 30% of patients treated with bevacizumab (240) (245) (246). Other antineoplastic agents are known to modulate blood pressure, but their effect and clinical significance are far less than what is observed for bevacizumab (240). For example, although changes in blood pressure have been observed following paclitaxel administration, the product monograph indicates that patients are usually asymptomatic (247).

2.1.6 Thrombosis

The formation of blood clots leading to obstruction of the blood flow can occur during blood vessel injury or when the composition of the blood is altered. Different pharmacological agents may damage vessels or affect the pro-thrombotic actions of blood factors leading to blood vessel obstruction and hypoxia. In severe cases of oxygen deprivation, thrombosis may even result in myocardial ischeamia and infarction (248). Complications may also arise when a detached intravascular mass cause vascular occlusion in distant parts of the body. Arterial thrombosis generally consists of platelet adherence to rupture endothelial surfaces whereas venous thomboses are often enriched in fibrin and erythrocytes and can occur in absence of vessel damage (249).

On its own, a cancer diagnosis is associated with a 4.1 fold risk of thrombosis increasing up to 6.5 fold in patients receiving chemotherapy (250). Platinum-based chemotherapeutic regimens (251) and bevacizumab (252) are among the therapies with increased risk of thromboembolism. Female breast cancer patients treated with chemotherapy are at increased risk of thromboembolic events, especially in postmenopausal patients at late stages of the disease (253) (254). However, in comparison to other neoplasms, the risk appears to be lower in breast cancer populations (255) (256) (257) (258). Contemporary pharmacological regimens and patient-specific risk factors may

contribute to the observed variation in risk. The risk of arterial and venous thrombosis is higher in breast cancer patients with metastatic disease (253) in part due to the increase in tumor burden, treatment aggressiveness and other predisposing factors such as immobilization (259). Different mechanisms of the thrombogenic effect of therapies have been proposed, but the exact etiology of the disease remains poorly understood. Impairment of vitamin K metabolism, endothelial cell injury, direct platelet activation, reduced fibrinolytic activity and the release of pro-coagulant from the dying tumor cells have all been suggested as mechanisms for drug-induced thrombosis.

2.1.7 Artherosclerosis

The process of atherosclerosis is promoted by endothelial injury and/or excess of circulating lipids (260). Low-density lipoproteins (LDL) accumulate in the arteries where they get oxidized and engulfed by foam cells (261). High-density lipoproteins (HDL) decrease the risk of atherosclerosis by preventing the oxidation of LDL and by removing cholesterol from foam cells. Early sub-endothelial accumulation and lipid deposits in the form of atherosclerotic lesions and fatty streaks eventually progress to vascular responses involving inflammation and monocytes (262) (263). The growth of the atherosclerotic plaques is further stimulated by smooth muscle proliferation and migration from the media to the intima. The vasculature attempts to adapt to the plaque formation, which leads to

vasodilation and intramural calcification of the endothelial walls. Breast cancer patients were reported to have higher coronary artery calcium scores in comparison with a cohort of healthy women (264). Platinum-based chemotherapies, such as cisplatin, have been shown to influence arterial stiffness via vascular endothelial dysfunction and ultimately increase the risk of developing atherosclerosis and cardiovascular diseases (265). Treatment with etoposide has also been associated with increased atherosclerotic risk in testicular cancer patients (266). Plaque rupture, calcified nodules and plaque erosion are responsible for most coronary events, with coronary vasospam playing a role in the pathophysiology (267). Vascular occlusion and its associated decrease in blood supply can lead to myocardial ischemia and infarction (248). Lipid levels, homocysteine, C-reactive protein, glycosylated hemoglobin and ferritin have all been used as markers to predict cardiovascular events associated with atherosclerosis (268) (269). These laboratory parameters have also been used to determine the cardiovascular risks associated with various therapies, including progression of atherosclerosis in breast cancer patients following anthracycline therapy (270). The negative impact of combined therapies on laboratory parameters has also been evaluated in the context of colorectal cancer. A combination of bevacizumab, oxaliplatin, 5-fluorouracil and leucovorin was shown to modulate favorable effects on homocysteine and LDL cholesterol concentrations but was also associated with increased ferritin and glycosylated hemoglobin which are considered negative risk factors for atherosclerosis (271). Limited information is available about the effect of specific chemotherapy or target agent on laboratory parameters, atherosclerosis and long-term cardiovascular health since most treatment regimens are composed of a

combination of therapies and clinical trials have usually limited follow-up time. Moreover, when evaluating risks, the population of interest must be kept in mind. Since 99% of new invasive breast cancer cases are expected to be female patients (230,480 out of 232,620) (272) and the risk of atherosclerosis differs between genders (273), caution must be applied when conclusions are drawn from trials in different patient populations.

2.1.8 Ischemia, coronary heart diseases, and myocardial infarction

Angina pectoris is one of the most common cardiovascular events reported by cancer patients (274). Chest pain is the result of underlying myocardial ischemia generally attributable to obstruction or spasm of the coronary arteries (275). Breast cancer patients were reported to be at higher risk of coronary heart disease than healthy, asymptomatic controls (264). Sustained interruption of blood supply can cause irreversible damage to the myocardium and lead to an infarction. The clinical presentation may be symptomatic or silent and can even lead to acute left ventricular failure or sudden death. Various blood markers of myocardial injury have been used in the diagnosis and risk evaluation of myocardial infarction (MI). Measurements of total creatine kinase and isoenzyme MB was the goal standard test for acute MI in the mid-1990s as levels rise 4 to 9 hours after the onset of chest pain, with a peak at 24 hours (276) (277). Since elevation of creatine kinase levels is not specific to cardiac injury and may be observed during musculoskeletal injuries

and other disorders, an array of biochemical markers of myocardial damage are now used to confirm the diagnosis (278). Other markers include oxygen-binding protein myoglobin, Troponin proteins T and I, C-reactive protein and B-type natriuretic peptide (276). Troponin I was shown to be particularly useful in the monitoring of cardiovascular complications during and after chemotherapy treatment (279). Although anthracycline is the class of antineoplastic agents with the highest association with severe cardiovascular outcomes, other cancer therapies increase the risk of coronary heart diseases and myocardial infarction. Cisplatin has been shown to cause chest pain and elevation of cardiac enzymes indicative of MI (280). Etoposide also predisposes patients who have previously undergone chemotherapy or mediastinal radiation to infarction (281) (282). Ischemic syndrome, presenting as angina pectoris and/or acute MI, has been reported following treatment with 5-fluorouracil and a re-challenge with the drug reproduces the initial ischemia event (283). Although the administration of pro-drug capecitabine, which is enzymatically converted to 5-fluorouracil, is thought to be less toxic than direct 5-flurouracil treatment, this drug is also associated with increased incidence in angina and MI (284). Treatment with vinca alkaloids such as vinorelbine has been similarly associated with these cardiac events (285) (286), which were shown to be more likely to occur in women (287). Some small molecule inhibitors are also associated with increased risk. Erlotinib was shown to increase the risk of MI and stroke, whereas sorafenib was associated to higher incidence of cardiac ischemia in patients with non-small cell lung carcinoma (NSCLC) and renal cell carcinoma, respectively (288).

2.1.9 Left ventricular dysfunction and heart failure

Left ventricular dysfunction with resulting congestive heart failure is often the ultimate consequence of a variety of cardiovascular events. The American College of Cardiology Foundation and the American Heart Association have defined heart failure as a complex syndrome resulting from any structural, or functional heart complications, which impairs ventricular filling or blood ejection (289). Ischemia and prior MI constitute the most common etiology (290). Ventricular dilation post-MI alters the left ventricular ejection fraction, contributes to mechanical inefficiency and is a precursor of heart failure. Anthracyclines are the class of antineoplastic agents associated with the highest incidence of heart failure, with doxorubicin being the leading causative agents with 26% to 48% incidence depending on the cumulative dose (291) (292) (293) (294). Heart failure following treatment with other anthracyclines, such as epirubicin and idarubicin, appears to be less frequent (274). High levels of B-type natriuretic peptide have been used as a marker of impaired left ventricular function during anthracycline therapy (295). Clinical manifestations of heart failure and left ventricular dysfunction have been described following treatment with other classes of antineoplastic agents including alkylating agents cyclophosphamide (296) (297) (298) and ifosfamide (299), antimetabolite 5-fluorouracil (300), antibiotic mitomycin (175), anti-mitotic agent docetaxel (301) (302) and monoclonal antibody trastuzumab (303). The risk associated with trastuzumab is especially high when the drug is administered in conjunction with other cardiotoxic therapies. Lapatinib, another

Her-2 targeted therapy, was shown to have some cardiotoxic potential. This small molecule inhibitor can decrease left ventricular ejection fraction in patients, but the cardiac effects of lapatinib are generally reversible and non-progressive in contrast to irreversible anthracycline-induced cardiac failure (304). The symptoms appear to occur at similar rates in patients with or without prior anthracyclines or trastuzumab treatment (305).

2.2 Cardiotoxicity and oncology drugs

Table *8* provides a descriptive overview of the cardiovascular events that have been reported with exposure to chemotherapies, immune therapies and small molecule inhibitors approved by the FDA as cancer treatments before June 31, 2013. This list only enumerates events summarised in the FDA-approved prescribing information or recorded in clinical trials. It is not a quantitative assessment of the level of risk associated with each drug product.

Table 8: Enumeration of cardiovascular events reported with exposure to chemotherapies, immunotherapies and small molecule inhibitors approved by the FDA as cancer treatments before June 31, 2013

Drug	Cardiac effects
5-Fluorouracil (5-FU)	Ischemic syndrome, angina pectoris, acute MI, arrhythmia (ventricular tachycardia), pulmonary edema, cardiac arrest, HF, pericarditis, coronary spasm, ventricular ectopy (283) (306) (307) (308) (309) (310)
Afatinib	Decrease in left ventricular ejection fraction (311)
Aflibercept	Hypertension, transient ischemic attacks, venous thromboembolism, cerebrovascular accident, angina pectoris (312) (313)
Aldesleukin	Hypotension, capillary leak syndrome, peripheral edema, cardiac arrhythmias (supraventricular or ventricular tachycardia, atrial fibrillation, bradycardia), vasodilatation, HF, angina pectoris, MI, hypotension (310) (314) (315)
Alemtuzumab	Hypotension, hypertension, arrhythmia, HF (316) (317)
Asparaginase	Serious thrombotic events (318)
Axitinib	Hypertension, arterial and venous thrombotic events, transient ischemic attack, cerebrovascular accident, MI, HF (319) (320)
Azacitidine	Peripheral edema, angina pectoris, Atrial fibrillation, cardiac murmur, hypertension, tachycardia, hypotension, HF, cardiac failure congestive, cardio-respiratory arrest, congestive cardiomyopathy (321)
Bendamustine	Peripheral edema, tachycardia, angina pectoris, hypotension, hypertension and HF (322) (323)
Bevacizumab	Hypertension, arterial and venous thromboembolic events, hypotension, deep thrombophlebitis, HF, cardiac ischemia, stroke, MI, left ventricular dysfunction, angina pectoris (324) (325) (326) (327) (328) (329) (330) (331) (332)
Bleomycin	Pericarditis, angina pectoris, myocardial ischemia, MI, hypotension, cerebrovascular accident (333) (334) (335) (336) (337) (338) (339)
Bortezomib	Hypotension, HF, cardiogenic shock, left ventricular dysfunction, angina pectoris, atrial fibrillation aggravated, atrial flutter, bradycardia, sinus arrest, cardiac tamponade, cardiopulmonary arrest, MI, pericarditis, pericardial effusion, torsades de pointes, ventricular tachycardia, cardiac amyloidosis, complete atrioventricular block, myocardial ischemia (340)
Bosutinib	Edema, pericardial effusion, angina pectoris, pericarditis, QTc prolongation (341) (342)
Brentuximab vedotin	Peripheral edema, arrhythmia (supraventricular arrhythmia, tachycardia, but no clinically relevant QTc prolongation) (343) (344)
Busulfan	Tachyarrhythmias, hypertension or hypotension , edema, thrombosis, angina pectoris, vasodilatation, atrial fibrillation, cardiac tamponade, heart block, HF, left ventricular dysfunction (oral), pericardial and endomyocardial fibrosis (345) (346) (347) (348)
Cabazitaxel	Peripheral edema, arrhythmia, hypotension, 5 cardiac related death in TROPIC trial (ventricular fibrillation, sudden cardiac death, cardiac arrest) (349)
Cabozantinib	Hypertension, venous and atrial thromboembolism, MI, cerebral infarction, cardiac arrest (350)
Capecitabine	Similar profile to 5-FU, edema, venous thrombosis, myocardial ischemia, MI, angina pectoris, arrhythmias (tachycardia, bradycardia, atrial fibrillation, ventricular extrasystoles, cardiac arrest, HF, sudden death, deep vein thrombosis, cerebral vascular accident, cardiomyopathy, myocarditis, pericardial effusion, thrombophlebitis, thrombophlebitis (351) (352) (353) (354) (355)
Carboplatin	HF, embolism, cerebrovascular accidents, hypertension, hypotension (356)
Carfilzomib	Peripheral edema, hypertension, left ventricular dysfunction, myocardial ischemia, fatal HF, acute pulmonary edema, pulmonary arterial hypertension (357) (358)
Carmustine	Hypotension, tachycardia, deep thrombophlebitis, angina pectoris (359)
Cetuximab	Cardio-pulmonary arrest, myocardial ischemia, arrhythmia, infusion-related reactions :

	hypotension, MI, cardiac arrest (360)
Chlorambucil	Non-significant cardiovascular effect documented to date
Cisplatin	Elevated cardiac enzymes, angina pectoris, palpitations, HF, supraventricular tachycardia, bradycardia, ST-T wave changes, left bundle branch block, atrial fibrillation, acute ischemic events, late complications: hypertension, left ventricular hypertrophy, myocardial ischemia, ischemic cardiomyopathy, MI, thrombosis, stroke, hypotension, thrombophlebitis (280) (310) (361) (362) (363) (364) (251)
Cladribine	Edema, ischemia, tachycardia, thrombosis, HF (365) (366)
Clofarabine	Capillary leak syndrome, tachycardia, hypotension, hypertension, pulmonary edema, pericardial effusion, left ventricular pressure increased (367)
Crizotinib	Edema, bradycardia, pulmonary embolism, QTc prolongation, syncope, angina pectoris (368)
Cyclophosphamide	HF, myocarditis, pericarditis, increased LV wall thickness with hemorrhagic myocardial necrosis, pericardial effusion (progressing to cardiac tamponade), myocardial hemorrhage, arrhythmias (supraventricular and ventricular arrhythmias (atrial fibrillation, flutter, severe QT prolongation with ventricular tachyarrhythmia)), bradycardia, tachycardia, palpitations, cardiogenic shock, cardiomyopathy, carditis, atrioventricular block (296) (297) (369) (370) (371) (372) (373)
Cytarabine	angina pectoris, pericarditis, pericardial effusion, cardiac tamponade, bradycardia, cardiomyopathy, acute cardiopulmonary arrest, cardiomegaly (374) (375) (376) (377) (378) (379)
Cytarabine liposomal	Peripheral edema, tachycardia, hypotension, hypertension, syncope (380)
Dabrafenib	Cardiomyopathy, decrease in left ventricular ejection fraction, HF, deep vein thrombosis, pulmonary embolism, hypertension, hypotension (381)
Dacarbazine	Facial flushing, ECG abnormalities, orthostatic hypotension (382)
Dactinomycin	Venoocclusive disease (383)
Dasatinib	QTc prolongation, angina pectoris, pericardial effusion, left ventricular dysfunction, HF, cardiomyopathy, diastolic dysfunctions, fatal MI, pericardial effusion, palpitations, pulmonary arterial hypertension (384) (385)
Daunorubicin	ECG abnormalities (supraventricular tachycardia, S-T wave changes, atrial or ventricular extra-systoles), HF, cardiomyopathy, MI, myocarditis, pericarditis (386) (387) (388)
Daunorubicin liposomal	Edema, angina pectoris, hypertension, palpitation, syncope, tachycardia, decrease in left ventricular ejection fraction, HF, cardiomyopathy, atrial fibrillation, cardiac arrest, MI, pericardial effusion, pericardial tamponade, ventricular extrasystoles (389) (390) (391) (392)
Decitabine	Peripheral edema, cardiac murmur, hypotension, tachycardia, angina pectoris, pulmonary edema, hypertension, HF, cardio-respiratory arrest, pulmonary embolism (393)
Denileukin diftitox	Capillary leak syndrome (with fatalities), hypotension, angina pectoris, tachycardia, MI, HF (394) (395)
Docetaxel	Decrease in left ventricular ejection fraction, hypotension, conduction abnormalities (cardiac tamponade, sinus tachycardia, atrial flutter, atrial fibrillation, dysrhythmia) angina pectoris, cardiovascular collapse, HF, MI, thrombophlebitis, left ventricular dysfunction, pulmonary edema, hypertension (396) (397) (301) (398). Potentiate HF when in combination with anthracyclines (399)
Doxorubicin	Arrhythmia (atrial fibrillation, atrioventricular block, heart block, ventricular tachycardia, bradycardia, extrasystoles, sinus tachycardia), decrease in left ventricular ejection fraction, HF, cardiomegaly, edema, pleural effusion, pulmonary edema, pericarditis-myocarditis, MI (207) (292) (294) (400) (401) (402) (403) (404) (405)
Doxorubicin liposomal	Peripheral edema, HF, left ventricular dysfunction, vasodilation, tachycardia, deep thrombophlebitis, hypotension, cardiogenic shock, cardiac arrest, angina pectoris, bundle branch block, cardiomegaly, cardiomyopathy, thrombosis (406) (407) Lower incidence in HF and myocardial damage than doxorubicin (408) (409) (410) (233).
Epirubicin	Less cardiotoxic than doxorubicin (411) (412). Decrease in left ventricular ejection fraction, HF, arrhythmia (sinus tachycardia, non-specific ST-T wave changes, premature ventricular

	contractions, ventricular tachycardia, bradycardia, atrioventricular and bundle-branch block), thromboembolism, thrombophlebitis, cardiomyopathy, myocarditis, pulmonary edema, pulmonary embolism (413) (414)
Eribulin	Peripheral edema, QTc prolongation (415) (416)
Erlotinib	Angina pectoris, peripheral edema, thrombosis, myocardial ischemia, MI, cerebrovascular accidents including cerebral hemorrhage, arrhythmias, syncope (417) (418)
Etoposide	Hypotension, myocardial ischemia, MI, vasospastic angina, tachycardia (337) (419) (420) (421)
Estramustine	Edema, HF, fatal MI, coronary ischemia, cerebrovascular accident, angina pectoris, flushing, thrombosis (422) (423)
Everolimus	Peripheral edema, hypertension, tachycardia, cardiac arrest, HF, angina pectoris, deep vein thrombosis, edema, hypotension, palpitation, syncope, venous thromboembolism, pulmonary embolism, MI (424)
Floxuridine	Myocardial ischemia (425)
Fludarabine	Edema, angina pectoris, arrhythmia, cerebrovascular accident, HF, MI, supraventricular tachycardia, deep vein thrombosis, phlebitis, aneurysm, transient ischemic attack, hypotension, pericardial effusion (426) (427)
Gefitinib	Peripheral edema, non-clinical (*in vitro* and *in vivo*) inhibition of QT interval (428)
Gemcitabine	Peripheral edema, edema, capillary leak syndrome, arrhythmia, supraventricular arrhythmias, cerebrovascular accident, HF, hypertension, hypotension, pulmonary edema, MI (429)
Gemtuzumab ozogamicin	Cerebral hemorrhage, hypertension, hypotension, pulmonary edema, tachycardia, bradycardia (hypersensitivity reactions) (430)
Hydroxyurea	Edema (431)
Ibritumomab	Hypertension, pericarditis, severe infusion reaction: MI, ventricular fibrillation, cardiogenic shock, hypotension (432)
Idarubicin	HF, transient ECG abnormalities (supraventricular tachycardia, S-T wave changes, atrial or ventricular extrasystoles, atrial fibrillation), decrease in left ventricular fraction, angina pectoris, MI, cardiomyopathy, myocarditis (433) (434)
Ifosfamide	HF, arrhythmia (atrial/supraventricular tachycardia, atrial fibrillation, atrial flutter, pulseless ventricular tachycardia, decreased QRS voltage and ST-segment or T-wave changes, bradycardia, bundle branch block, extrasystoles), fatal cardiomyopathies, increased heart weight, small pericardial effusions, fibrinous pericarditis, epicardial fibrosis, hypotension, angina pectoris, palpitations, capillary leak syndrome, cardiogenic shock, decrease in left ventricular ejection fraction, hypertension, hypotension, myocardial hemorrhage, myocarditis, MI, subendocardial hemorrhage and petechial lesions in the epicardium (299) (435) (436)
Imatinib	Edema, pericardial effusion, peripheral edema, pulmonary edema, angina pectoris, hypotension, palpitation, flushing, arrhythmia, atrial fibrillation, tachycardia, cardiac tamponade, acute coronary syndromes, HF, left ventricular dysfunction, cardiogenic shock, hypereosinophilic cardiac toxicity, hypertension, MI, pericarditis, thrombosis (437) (438) (439) (440)
Interferon alfa-2a	Myocardial ischemia, MI, arrhythmia, sudden death, cardiomyopathy, left ventricular dysfunction, HF (441) (442) (443) (444) (445)
Ipilimumab	Myocarditis, pericarditis (446)
Irinotecan	Vasodilatation, edema, hypotension, thromboembolic events, bradycardia, arterial thrombosis, cardiac arrest, MI, myocardial ischemia, thrombophlebitis, thrombosis (447) (448)
Ixabepilone	Edema, angina pectoris, atrial flutter, cardiomyopathy, hypotension, thrombosis, embolism (449). In combination with capecitabine: Myocardial ischemia, MI, ventricular dysfunction, supraventricular arrhythmia (450)
Lapatinib	Less cardiotoxic than trastuzumab. Asymptomatic decrease in left ventricular ejection

	fraction, QTc prolongation (105) (305) (451) (452)
Lenalidomide	Peripheral edema, edema, deep vein thrombosis, hypertension, palpitations, pulmonary embolism, thromboembolic complications, atrial fibrillation, syncope, cerebrovascular accident, tachycardia, angina pectoris, bradycardia, cerebral ischemia, MI, HF, cardiac arrest, cardiogenic shock, pulmonary edema, cardiorespiratory arrest, orthostatic hypotension, thrombophlebitis (453) (454) (455) (456) (457)
Lomustine	Non-significant cardiovascular effect documented to date
Mechlorethamine	Thrombosis, thrombophlebitis (458) (459)
Melphalan	Hypersensitivity (tachycardia, edema, hypotension), atrial fibrillation, cardiac arrest, angina pectoris, hypertension, MI (310) (460) (461)
Mercaptopurine	Non-significant cardiovascular effect documented to date
Methotrexate	Vasculitis, syncope, supraventricular and ventricular arrhythmias, pericarditis, pericardial effusion, hypotension, thromboembolic events, (462) (463) (464) (465) debatable effect on MI and ischemic heart disease. May have some cardioprotective effect (466) (467) (468)
Mitomycin	HF, hypertension (469) (470) (471)
Mitoxantrone	Less cardiotoxic than doxorubicin (472) (473) (474). Edema, arrhythmia, asymptomatic ECG changes (non-specific changes, sinus bradycardia, sinus tachycardia, atrioventricular block), HF, left ventricular dysfunction, hypertension, angina pectoris, pericarditis-myocarditis, hypotension (475) (476) (477)
Nab-Paclitaxel	Similar to non-albumin bound formulation. Abnormal ECG, peripheral edema, HF, hypotension, chest pain, cardiac arrest, supraventricular tachycardia, thrombosis, pulmonary thromboembolism, pulmonary emboli, hypertension, myocardial ischemia, MI, hypotension, edema, left ventricular dysfunction, atrioventricular block, bradycardia, stroke (478) (479)
Nelarabine	Peripheral edema, edema, hypotension, tachycardia, angina pectoris (480)
Nilotinib	Peripheral edema, hypertension, arterial stenosis, QTc prolongation, sudden death, ischemic heart disease, peripheral arterial occlusive disease, ischemic cerebrovascular events, angina pectoris, arrhythmia (AV block, atrial fibrillation, bradycardia, cardiac flutter, extrasystoles, tachycardia), palpitations, flushing, pericardial effusion, aortic valve sclerosis, artheriosclerosis, HF, cardiomegaly, MI, pulmonary edema (384) (481) (482) (483) (484) (485)
Ofatumumab	Peripheral edema, hypertension, hypotension, tachycardia, Infusion-related reactions : hypertension, hypotension, syncope, myocardial ischemia, MI (486)
Oxaliplatin	Edema, angina pectoris, peripheral edema, flushing, thromboembolism, hypertension, tachycardia (487)
Paclitaxel	Flushing, abnormal ECG, edema, hypotension, bradycardia, tachycardia, hypertension, atrioventricular and bundle branch blocks, syncope, venous thrombosis, arrhythmia, atrial fibrillation, cardiac ischemia, HF, hypertension, left ventricular dysfunction, myocardial ischemia, MI, pulmonary embolism (235) (236) (488) (489) (490) (491)
Panitumumab	Peripheral edema, infusion-related hypotension, pulmonary embolism (492)
Pazopanib	Hypertension, bradycardia, peripheral edema, angina pectoris, left systolic dysfunction, venous thrombosis, ischemic heart disease, MI, QTc prolongation, transient ischemic attacks, HF, torsades de pointes, arterial and venous thromboembolic events, cerebral hemorrhage, cerebrovascular accident (493) (494) (495) (496)
Pegaspargase	Edema, thrombosis, hypotension (hypersensitivity), tachycardia (497)
Pemetrexed	Edema, arrhythmia, angina pectoris, supraventricular arrhythmia, ventricular tachycardia, syncope, hypertension, peripheral ischemia and edema, pulmonary embolism (498) (499)
Pentostatin	Angina pectoris, facial edema, hypotension, peripheral edema, arrhythmia, atrioventricular block, bradycardia, cardiac arrest, HF, hypertension, deep thrombophlebitis, pericardial effusion, tachycardia, sinus arrest, syncope, vasculitis, ventricular extrasystoles (500) (501)
Pertuzumab	Asymptomatic left ventricular systolic dysfunction, cardiomyopathy, HF, decrease in left ventricular ejection fraction (502) (503) (504) (505) (506)
Pomalidomide	Peripheral edema, deep venous thrombosis, pulmonary embolism, atrial fibrillation (507) (508)

Ponatinib	Vascular occlusion events (which led to market suspension in US on October 31, 2013) (509) hypertension, peripheral edema, left ventricular dysfunction, HF (including fatalities), pulmonary edema, cardiogenic shock, ischemia, MI, stroke, arrhythmia (symptomatic bradyarrhythmias, supraventricular tachyarrhythmias), heat block, QTc prolongation (510) (511)
Pralatrexate	Edema, tachycardia, cardiopulmonary arrest (512) (513)
Procarbazine	Edema, flushing, hypotension, syncope, tachycardia, hypertension, Raynaud-like syndrome (514)
Regorafenib	Hypertension, myocardial ischemia, MI, bradycardia (515) (516) (517)
Rituximab	Peripheral edema, hypertension, hypotension, flushing, arrhythmias, ventricular fibrillation, angina pectoris, MI, ventricular tachycardia, cardiogenic shock, HF, atrial fibrillation (518) (519) (520) (521) (522)
Romidepsin	ST-T wave changes, hypotension, QTc prolongation, ventricular tachycardia, sudden death, angina pectoris (523) (524) (525) (526)
Sorafenib	Hypertension, myocardial ischemia, MI, HF, flushing, ECG changes, QTc prolongation, peripheral edema, angina pectoris, edema, supraventricular and ventricular arrhythmias, syncope, atrial fibrillation, cardiopulmonary failure, cardiogenic shock (527) (528) (529) (530)
Streptozocin	Hypotension (531)
Sunitinib	Hypertension, peripheral edema, left ventricular dysfunction, fatal HF, angina pectoris, venous thrombosis, deep vein thrombosis, pulmonary embolism, ECG changes (axis or QRS amplitude, ST or T wave, QTc prolongation, torsade de pointes), atrial flutter, cardiomyopathy, MI (532) (533) (534) (535) (536) (537)
Temozolomide	Peripheral edema (538)
Temsirolimus	Edema, peripheral edema, angina pectoris, pericardial effusion, hypertension, venous thromboembolism, thrombophlebitis, infusion related hypotension (539) (540)
Teniposide	Hypotension, thrombophlebitis, one episode of sudden death attributed to probable arrhythmia and intractable hypotension, hypersensitivity reactions : tachycardia, hypertension (541) (542) (543)
Thalidomide	Edema, thromboembolic complications, hypotension, peripheral edema, facial edema, bradycardia, hypertension, peripheral vascular disorder, tachycardia, vasodilation, angina pectoris, atrial fibrillation, cerebral ischemia, cerebrovascular accident, syncope, heart arrest, MI, murmur (544) (545) (453) (546) (547)
Thioguanine	Non-significant cardiovascular effect documented to date
Thiotepa	Cardiac arrest, Abnormal ECG (tachycardia), cardiomyopathy, myocarditis, HF (548)
Topotecan	Angina pectoris, cardiac arrest (549)
Tositumomab	Hypotension, peripheral edema, angina pectoris, vasodilatation (550)
Trametinib	Hypertension, cardiomyopathy, bradycardia, left ventricular dysfunction, venous thromboembolism, HF (551) (552) (553)
Trastuzumab	Decrease in left ventricular ejection fraction, left ventricular dysfunction, edema, HF, tachycardia, hypertension, arrhythmia, palpitation, cardiomyopathy, exertional dyspnea, cardiac death, pericardial effusion, syncope, vascular thrombosis, ventricular dysfunction, volume overload (303) (554) (555) (556) (557) (558) (559) (560) (561) (562) (563) (564)
Trastuzumab-emtansine	Peripheral edema, hypertension, left ventricular systolic dysfunction, decrease in left ventricular ejection fraction, QTc prolongation (565) (566) (567) (566) (568) (569) (570)
Valrubicin	Angina pectoris, vasodilatation, peripheral edema (571) (572)
Vandetanib	Hypertension, QTc prolongation, HF, ischemic cerebrovascular events, torsades de pointes, ventricular tachycardia (573) (574) (575) (576)
Vemurafenib	Peripheral edema, QTc prolongation, atrial fibrillation, hypotension, vasculitis, cardiac tamponade (577) (578) (579)
Vinblastine	Hypertension, angina pectoris, cerebrovascular accident, coronary ischemia, abnormal ECG, MI, myocardial ischemia, Raynaud's phenomenon, vasoocclusive complications (580) (581) (582)

Vincristine	Edema, hypertension, hypotension, MI, myocardial ischemia, vasoocclusive complications (521) (582) (583) (584) (585) (586)
Vincristine liposomal	Cardiac arrest, hypotension (587)
Vinorelbine	Angina pectoris, vasoocclusive complications (thromboembolism, pulmonary embolism), myocardial ischemia, flushing, vasodilatation, hypertension, hypotension, MI, pulmonary edema, tachycardia. (582) (588) (589) (590)
Vismodegib	Atrial fibrillation, cardiac flutter, HF, restrictive cardiomyopathy, angina pectoris, MI, left ventricular dysfunction, fatal case of ischemic stroke (591) (592) (593)
Vorinostat	Peripheral edema, transient electrocardiographic changes (QTc prolongation, ST segment and T wave changes), pulmonary embolism, deep vein thrombosis, edema, angina pectoris, MI, ischemic stroke, hypertension, syncope, vasculitis (594) (595) (596)

2.3 Prospective surveillance of drug-induced cardiotoxicity

Although cardiotoxicity was identified as a potential adverse effect of chemotherapies as early as 1967 (597), the complete cardiovascular profile of a number of oncology drugs are not well recognised by many physicians (598). Since adverse reactions are likely to affect patient outcome and may be the dose limiting factor in cancer treatment (599), understanding these effects is of the utmost importance to their successful management. Each agent has a distinct cardiotoxicity profile as well as the ability to potentiate the cardiovascular effect of other chemotherapies (600). The cumulative incidence of treatment-related cardiovascular events may be as high as 33% following exposure to adjuvant therapies in a breast cancer (BC) setting (601). This toxicity can lead to severe morbidity among survivors (176) and may have more impact on mortality than BC itself (602) (603) (604). In the early days of cancer treatment, the cardiovascular effects of therapies were masked by the limited life expectancy of patients diagnosed with metastatic

disease. As innovative targeted-therapies were developed and screening programs established, the prognosis of breast cancer improved dramatically (166) which resulted in an increased awareness of the cardiotoxicity profile of anticancer drugs. The clinical impact on BC survivors is particularly relevant considering that the affected population is generally older and more prone to cardiovascular diseases (167). Yet, validated screening algorithms and requirements for cardiac function before, during and after breast cancer treatment are lacking. Thus far, there are no official practice guidelines specific to the post-treatment monitoring of the cardiovascular health of breast cancer survivors. Patients could benefit from being carefully monitored and assessed for cardiovascular risk factors and comorbidities, especially if concomitant cardiotoxic chemotherapies are administered. There was an attempt in 2005 by the American Society of Clinical Oncology (ASCO) to develop guidelines for the ongoing surveillance of cardiovascular complications in cancer survivors post chemotherapy and radiation treatments. The Board of Directors ultimately concluded that the gaps in the evidence needed to support a practice guideline prevented formal recommendations. A review of available clinical evidence was published instead (605). The considerable financial burden, low validation of clinical significance and effectiveness of various monitoring approaches, as well as the added anxiety to the patients are important drawbacks of cardiovascular monitoring that must be considered (606). Targeted monitoring approaches could maximize detection in high risk populations. A particular focus should be put on patients treated with drugs known for their adverse cardiovascular safety profile. Cardiac monitoring is especially important in patients receiving and patients who have received anthracycline therapy. The monitoring approach

selected should reflect the mechanism by which the therapy is known to exert its cardiotoxic effect. Different diagnostic and monitoring methods can be employed including echocardiography, radionucleotide angiography and, in rare circumstances, magnetic resonance imaging to assess myocardial function (607). Vital signs and electrocardiogram monitoring can be useful to screen for signs of conduction disturbances and cardiomyopathies (607). Based on its high sensitivity and specificity, compression ultrasonography is the primary diagnostic tool for thromboembolism. History of cardiovascular events should be considered and physical examinations focusing on signs and symptoms of cardiovascular events should be routinely performed. Biomarkers such as troponins and B–type natriuretic peptide may be used as predictors of cardiotoxicity associated with cancer therapies, although their clinical role is not well defined enough to include them as routine screening tools for that purpose (607). Notwithstanding its irregular use in clinical setting, troponin 1 has successfully been used to predict the development of cardiotoxicity in a cohort of 251 breast cancer survivors treated with trastuzumab (608). Endomyocardial biopsy is the gold standard for the diagnosis of heart failure but its use is limited by the invasiveness of the procedure (274). Other tests that have been used in surveillance of drug-induced cardiotoxicity include multi-gated acquisition scanning and exercise testing (609). Careful monitoring of patients is crucial for the early detection of warning signs of cardiotoxicity so that rapid risk mitigation strategy be implemented to prevent long-term deleterious effects, but additional studies are required to further validate the usefulness of any single or combination of tests for the prospective surveillance of drug-induced cardiac events.

2.4 Management and prevention of drug-induced cardiotoxicity

The use of pharmacological agents such as statins, β-blockers and angiotensin-converting enzyme inhibitors has been employed as a way to counteract the negative cardiovascular effects and manage drug-induced hyperlipidemia, hypertension, MI and HF (610). Angiotensin-converting enzyme inhibitors (611) and β-blockers (612) have been administered prophylactically to patients scheduled to receive anthracycline to reduce the incidence of drug-induced cardiomyopathies. Extending the infusion duration time with infusion pumps and dwelling catheters (613), decreasing total cumulative dose (291) (614) and administration of cardioprotective chelator agents such as dexrazoxane (293) (615) (616) (617) are all strategies employed to reduce chemotherapy-related cardiotoxicity. Aspirin has been shown to improve the survival of cancer patients experiencing thrombocytopenia and acute coronary syndromes without increasing the risk of bleeding (618). Discontinuation of the causative agents is often warranted as the cardiovascular symptoms often disappear once treatment is suspended. However, discontinuation of anti-angiogenic therapy due to a sudden increase in blood pressure is controversial as the appearance of high grade hypertension seems to coincide with treatment response (619). Cardiovascular hemodynamics and cardiac rhythm should be normalised or at least optimized if cardiotoxic agents are to be administered.

2.5 Risk factors

The cardiovascular risk factors affecting breast cancer patients reflect those present in the general population (620). Patient-related factors include prior history of cardiovascular diseases, age, body mass index and comorbidities such as diabetes (600) (294). Since more than half of breast cancer patients are over the age of 50, age definitely plays a role in the cardiovascular risk associated with breast cancer therapy (620). Decreased physical activity and associated weight gain were shown to have unfavorable consequences on the cardiovascular disease process in breast cancer patients (621). The Women's Healthy Eating and Living Study Group demonstrated that adjuvant therapy is associated with weight gains. Overweight postmenopausal women were shown to have higher levels of circulating sex hormones (622) and are also at increased risk of breast cancer (612) (623). Interventions such as increased exercise and reduction in body mass index can improve the overall cardiovascular health of breast cancer patients on adjuvant endocrine therapies (620).

Treatment-related factors can also influence the risk of drug-induced cardiovascular events. They include the cumulative dose, route of administration, schedule of delivery, sequence and combination of drugs, and prior radiotherapy or surgery. Prior mediastinal radiation is a risk factor for cardiovascular diseases in breast cancer patients. Cardiac

exposure to ionizing radiation in breast cancer patients treated with radiotherapy increases the risk of subsequent heart diseases for at least 20 years post-treatment (624). However, improvement in radiation techniques has led to decreased cardiac exposure during the last decades (625) and the lifetime risk of major coronary events following breast radiation is now typically around 0.3% (626). Risk factors include the side of the breast being irradiated (627), whether the patient is lying in prone or supine position (628), the mean dose to the heart (624) and whether the patient is receiving external versus intraoperative radiation therapy (629). Although cardiac complications are infrequently reported following mastectomies (630), thromboembolism is a known complication of surgical procedures (631), but venous thromboembolism prophylaxis is not routinely indicated for prevention in breast cancer patients undergoing surgery (632) (633). In their treatment decisions, physicians should consider underlying risk factors and balance them against the potential benefit expected from the chosen therapy. Long-term cardiac consequences should be considered despite the immediate need for an antineoplastic strategy.

2.6 Research rationale and objectives

Recognizing that drug-induced cardiotoxicity can lead to severe morbidity among survivors and impact mortality more than breast cancer itself (176), the overarching objective of this project was to determine which categories of antineoplastic drugs are of

most concern amongst breast cancer patients based on their cardiotoxic potential and pattern of use. To address this research question, three specific objectives were set, each of which was addressed in a manuscript format.

The first objective was to review molecular and physiological mechanisms of cardiovascular effects associated with endocrine therapies to better understand the cardiotoxicity profile of estrogen-targeted therapies (Chapter 3). It was anticipated that SERMs would demonstrate cardioprotective mechanisms, while AIs would have a negative impact on the cardiovascular system. If, indeed, a class of estrogen-targeted therapy is associated with a less favorable risk profile at the molecular level, then further investigation in clinical or observational settings is warranted.

To confirm these molecular findings, the second objective was to evaluate the cardiovascular risks associated with estrogen-targeted therapies in a nested case-control study (Chapter 4). As with the first manuscript, AIs were expected to be associated with a less favorable safety profile than SERMs. If AIs are shown to be more cardiotoxic independently of other risk factors in a heterogeneous population of breast cancer patients, this analysis will corroborate the findings of another recent observational study (634) and inform treatment decisions.

The third and final objective was to investigate the pattern of use of various chemotherapies, hormone therapies, targeted agents, and immunotherapies and determine the extent of off-label use of these therapies. Off-label prescribing practice was expected to be common and evidence-based. If this hypothesis is supported, then a comprehensive approach, covering all antineoplastic agents administered, should be adopted in the evaluation of drug-induced adverse events, as these unconventional breast cancer treatments have their own inherent, and possibly incompletely characterized, safety profiles.

Since breast cancer patients are treated with a variety of antineoplastic agents, regardless of their indication for use, the importance of evaluating the cardiovascular risks associated with a wide range of antineoplastic agents including alkylating agents, antimetabolites, anti-tumor antibiotics, topoisomerase inhibitors, anti-mitotic agents, small molecule inhibitors, immunomodulators and monoclonal antibodies is discussed in Chapter 6. Differences in risk profiles should be considered when weighing the relative risks and benefits to support informed decision making. Adverse reactions are likely to affect patient outcome and may be the dose-limiting factor in cancer treatment (599). Understanding prescribing practices and cardiovascular risks associated with therapies used in the treatment of breast cancer is of the utmost importance in the clinical management of

breast cancer survivors. This research will help support treatment decision as well as decrease cardiovascular morbidity and mortality in breast cancer survivors.

Chapter 3

Cardiovascular effects of estrogen-targeted therapy in breast cancer

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Description and statement of contributions of collaborators and co-author**s**

This manuscript describes the molecular mechanisms of cardiovascular effects of endocrine therapies and their clinical impact in breast cancer patients. An overview of the influence of estrogen on cardiovascular function is also provided with an emphasis on the consequences of SERM and AI treatment on cardiac health.

S. Hamel performed the literature search required for this manuscript, created all tables presented and wrote the text with occasional guidance from Dr. D. Krewski. Editing and revisions were completed with the assistance of Dr. D. Krewski, Dr. A. Krantis, Dr. D. McNair, Dr. D. Mattison, and Dr. N. Birkett.

Abstract

Estrogen-targeted therapies are considered standard of care in the treatment of estrogen receptor positive tumors. However the nature and extent of cardiovascular risk associated with these therapies remain a controversial issue among the scientific community. Although, tamoxifen is associated with increased incidence of stroke and thromboembolism (635) (636), cardioprotective properties have also been attributed to this antineoplastic drug (637). The aim of this report is to review the molecular and physiological mechanisms of cardiovascular effects attributable to different classes of endocrine therapies and their clinical impact. In particular, the role of estrogen on cardiac health is described with a focus on cardiovascular risks associated with selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs). Based on their mechanism of action, AIs are expected to be associated with a higher cardiovascular risk than SERMs. Since cardiovascular disorders are among the most prominent comorbidities in breast cancer patients, the potential benefit of therapy must be balanced with the long term risks when a treatment option is selected.

Introduction

Estrogen has been associated with the pathogenesis of both breast neoplasia and cardiovascular events (638). The observation that the risk of cardiovascular disease increases in postmenopausal women to the same levels found in men led to the hypothesis that estrogen could exert a protective role on cardiac health (639). After menopause, the risk of artheriosclerosis increases by a factor of three whereas ovariectomy increases the risk six fold (640). The cardioprotective properties of estrogen were initially attributed to its beneficial effects on lipid metabolism (641), but there is increasing evidence that estrogen has a broader impact on cardiovascular health (642) (643). An extensive search of Medline, U.S. FDA clinical reviews, and drug/disease-state databases (UptoDate online, MICROMEDEX) was conducted to collect clinical and pre-clinical evidence of the cardiovascular effect of estrogen and ETs.

Estrogen and cardiovascular diseases

Several *in vitro* and *in vivo* assays as well as epidemiological studies have been used in attempt to characterise the cardiovascular effects of estrogen on the cardiovascular system. Estrogen was shown to play a role in the enhanced survival of endothelial cell, which could explain the atheroprotective effect of this hormone (644). Polymorphisms in

either subtypes of the estrogen receptor (ERα or ERβ) have been linked to both increased risk and severity of cardiovascular diseases (645) (646) (647) (648) (649). Reduction in estrogen receptor alpha (ERα) expression has been associated with the formation of atherosclerotic plaques and the development of coronary artery disease both in clinical trials (650) and *in vivo* studies (639) (651). ERβ has an anti-hypertrophic cardiac effect, whereas ERα has little impact on hypertrophic cardiomyopathy (650) (652) (653). Studies using ovariectomized female mice produced conflicting results in the cardiac hypertrophic role of estrogen; however, it should be noted that ovariectomy only reduces circulating estrogen levels by 50 to 80% and does not block the conversion of testosterone into estrogen (654) (655) (656) (657). The complete absence of estrogen production in aromatase knockout mice (658) leads to decreased cardiac function, protection from short-term cardiac ischemic injury (659) and cardiac hypertrophy (660). Many mechanisms have been suggested to explain the effect of estrogen on cardiac hypertrophy, including the regulation of calcium signaling (661), modulation of cellular pH (662), inhibition of calcineurin degradation (654), inhibition of apoptosis (663), and AKT signaling (664). Some studies have even suggested that the cardioprotective effect of estrogen is partially mediated in an estrogen receptor (ER) independent fashion (665).

Table 9: Molecular mechanisms of estrogen-mediated cardiac effects

Mechanism
Polymorphisms of estrogen receptor
Expression estrogen receptors (ERα, ERβ)
Scavenging lipid peroxyl radicals
Activation of endothelial NO synthase via AKT signalling
Regulation of Ca^{2+} signalling
Modulation of cellular pH
Calcineurin degradation
Inhibition of apoptosis

Antioxidant properties have been attributed to estrogen through its scavenging effect on lipid peroxyl radicals (666). Estrogen deficiency has also been linked to the upregulation of the renin-angiotensin-aldosterone system, leading to high concentrations of aldosterone in serum (667) (668) (669), retention of sodium and water, increased blood volume, and elevated blood pressure (670). Estrogen may also exert its cardioprotective effects by influencing the synthesis of nitric oxide from the enzyme endothelial NO synthase (671), as demonstrated by the reduction of myocardial infarct size in both male and female dogs following acute estrogen treatment, an effect that is eliminated by concomitant treatment with NOS inhibitor (672).

Despite evidence of benefit from hormone-replacement therapy (HRT) in earlier epidemiological studies (673) (674) (675), the cardioprotective role of estrogen has been challenged by results from different randomized clinical trials, which demonstrated no

overall benefit on cardiovascular health (676) (677) (678). The Women's Health Initiative (WHI) trial reported an increase in cardiovascular disease frequency in postmenopausal women on estrogen plus progestin HRT when compared to placebo (679) (680). Plus, the WHI estrogen alone trial failed to demonstrate protection against myocardial infarction or coronary death in healthy postmenopausal women (681). However, there was a slight decrease in coronary heart disease risk among women of 50 to 59 years of age receiving estrogen alone. This study was stopped prematurely due to an increase in the risk in stroke. These highly publicized studies caused widespread debate about the net effect of HRT on heart diseases. Some clarity began to emerge from the report of the WHI Coronary-Artery Calcium Study examining the effect of estrogen on coronary artery calcification. Women who were 50 to 59 years of age at randomization had significantly less coronary-artery calcification, a risk factor for atherosclerosis and future cardiovascular events, than women randomly assigned to receive placebo (682). The WHI trials suggest the importance of timing in HRT administration in that HRT may only be beneficial in preventing atherosclerosis if therapy is initiated before advanced atherosclerosis develops (683).

Table 10: Key cardiovascular findings in clinical trials of post-menopausal women treated with hormone replacement therapy (HRT)

Trial	Cardiovascular effect
WHI estrogen +Progestin HRT	↑coronary heart diseases
WHI estrogen alone	No protection against MI or coronary death
WHI estrogen alone - 50-59 year old	slight ↓ coronary heart disease, ↑ in stroke
WHI Coronary-Artery Calcium study - 50-59 year old	↓coronary-artery calcification

Estrogen has been linked to the regulation of serum lipid and cholesterol (684) (685) (686) as well as recovery from vascular injury (687). Based on a meta-analysis of 9 placebo-controlled trials, treatment with HRT was associated with increased venous thromboembolism and stroke (688), an observation supporting the negative recommendation on the use of HRT in the prevention of cardiovascular diseases in postmenopausal women (689). Yet, another more recent randomized trial has not shown any increase in mortality, myocardial infarction, heart failure, stroke or venous thromboembolism following 10 years of HRT (690). Nonetheless, estrogen has been shown to induce vascular smooth muscle relaxation and inhibition of platelet activation through the rapid release of nitric oxide (691) (692) ; this hormone is also thought to have significant effect on fibrinolysis activity (693) (694) (695). The route of administration and type of estrogen administered are thought to be key determinants of these estrogenic effects on the risk of venous thrombosis and stroke (696) (697) (401). More studies are required to determine the exact role of estrogen in cardiac pathogenesis. The molecular mechanisms of estrogen mediated cardiac effects and key cardiovascular findings in clinical trials are summarised in **Table *9*** and **Table *10***, respectively.

ESTROGEN-TRAGETED THERAPIES

Hormone-receptor positive breast cancer, defined on the basis of immunological expression of the ER, constitutes about 60% of breast cancer diagnosed in premenopausal women and up to 80% of cases arising after menopause (698). Even though ER status is not a direct predictor of prognosis, ER positive tumours are more likely to respond to a variety of hormonal treatments which may influence the risk of recurrence (699). Because the growth of ER positive breast cancer cells is dependent on estrogen stimulation, estrogen-targeted therapies such as selective estrogen-receptor modulators (SERMs) and aromatase inhibitors (AIs) have been developed and used in clinical settings.

SERMs antagonise the proliferative action of estrogen on breast cancer cells via direct interaction with the ER. However, cardiac myocytes and fibroblasts express functional ERs (700), which raise questions on the potential for effect of SERMs on cardiac function. Tamoxifen acts as a non-steroidal competitive antagonist on breast cancer cells, but has agonistic effects on bones (701) and lipids (702). This triphenylethylene also modulates partial agonistic effects on the uterus which are suspected to be responsible for the reported increased in uterine cancer following prolonged tamoxifen use. (703) The cardiovascular effects of SERMs have been investigated both *in vivo* and clinically. Although tamoxifen was reported to play a protective role on cardiovascular health (637), the effect

of long-term use on the heart and vasculature remains a controversial issue. Significant cardiac uptake of tamoxifen has been demonstrated using F-18 fluoro-tamoxifen and is thought to be the result of intracellular accumulation by cardiac myocytes (704).

The cardiovascular effects that have been reported following exposure to SERMs with a focus on molecular and cellular pathways potentially leading to the clinical outcome are summarized in **Table *11***.

Antioxidant-mediated cardioprotective effect of SERMs

Although tamoxifen has been shown to induce oxidative stress by generating reactive oxygen species and thiol depletion in a dose-dependent fashion in ER-negative human cancer cell lines (705), this drug was shown to protect against lipid peroxidation (706) (707). Prevention of oxidative degradation of lipids has been suggested to be an important factor driving the cardioprotective effect of tamoxifen (708), even if this drug was shown to increase renal lipid peroxidation in a mouse model (709). The phenolic metabolite of tamoxifen, 4-hydroxytamoxifen, was shown to have a direct antioxidant effect on membrane lipids and smooth muscle cells (710) by reacting quantitatively with hydroxyl free radicals (711). Tamoxifen and its metabolites are also thought to stabilise the

membrane against lipid peroxidation through a decrease in membrane fluidity (712). These antioxidant properties could lead to cardioprotection and benefits against atherosclerosis (713).

SERMs, lipid levels, and atherosclerosis

Together with its anti-oxidative properties, SERMs modulate their beneficial effect on atherosclerosis by modulating the level of circulating lipids. As a class effect, all SERMs decrease, to varying degrees, total circulating cholesterol by reducing LDL levels. In a double-blind, placebo-controlled study of postmenopausal breast cancer patients, total cholesterol and LDL levels decreased by 12% and 20%, respectively, after 2 years of tamoxifen treatment (714), with the effect being maintained after 5 years of treatment (715). Similar effects were observed in premenopausal breast cancer patients (716) and postmenopausal patients with node-negative neoplasms (717). Different mechanisms are thought to contribute to the decrease in lipid level observed after tamoxifen treatment. The drug can act directly as a sterol-Δ8,7-isomerase inhibitor and block the conversion of zymosterol into cholesterol (718) (719). Tamoxifen also affects the esterification of cholesterol by inhibition of Acyl-CoA cholesterol acyl transferase (720). In contrast to their effect on circulating cholesterol, SERMs were shown to increase triglyceride levels (721) (722) (723), but serum concentrations decreased after tamoxifen withdrawal (724). This

drug was shown to reduce circulating homocysteine (725) (726), thereby lowering the prevalence of a well-known risk factor for atherosclerosis (727) (728) .

The effect of SERMs on HDL levels remains a controversial issue. Tamoxifen was shown to affect HDL levels *in vitro* by increasing the synthesis of apolipoprotein A-I, the major component of HDL, in the liver through signalling via the ER (729). However, changes in HDL levels reported in clinical practice have been inconsistent (730). An increase (731), stable state (732) (733) and even a decrease (714) (734) (735) in HDL concentrations have been observed in patients treated with SERMs. In a comparative study, Toremifene, was shown to reduce total cholesterol and LDL levels but had an opposite effect to that of tamoxifen on HDL (734): Toremifene increased HDL levels by 14% whereas concentrations were decreased by 5% in patients treated with tamoxifen. The clinical significance of the effect of SERMs on lipid levels remains questionable as trials have yet to demonstrate a significant impact on the incidence of atherosclerosis. More studies are required to determine whether the effect of SERMs on lipid levels leads to changes in pathogenesis and symptoms associated with atherosclerosis.

SERMs and rhythm disturbances

Tamoxifen has been found to reduce the incidence of ventricular tachycardia as well as the incidence and duration of reversible ventricular fibrillation on ischemia and reperfusion in ovariectomized rats, suggesting that tamoxifen may have cardioprotective effects against myocardial ischemia reperfusion injury in rats (637). Although anti-estrogen therapies are generally thought not to cause rhythm disturbances and tamoxifen has rarely been linked to the development of symptomatic arrhythmias and torsades de pointes, few reports have raised concerns regarding QT interval prolongation following treatment with SERMs (736) (737) (738) (739). Inhibition of cardiac potassium currents, consistent with QT prolongation, has been reported following acute exposure to this SERM (740) (741) (742) (743). However, long-term treatment was shown to be associated with an increase in expression of potassium channels and potassium current density, which may explain the absence of cardiac arrhythmias with the long-term use of tamoxifen (736). The prescribing information for toremifene contains a warning for QTc interval prolongation in a dose- and concentration-related fashion (744). The QT interval prolongation reported in some clinical studies could be attributable to drug interactions (737). Tamoxifen and Toremifene are metabolised by cytochrome P450 enzymes such as CYP3A4, CYP2C9, and CYP2D6 (744) (745) (746) (747) and interactions with other drugs metabolised by these enzymes could induce depression of electrical impulse generated by the sinoatrial node (737) (748).

SERMs, platelet aggregation and thromboembolism

Conflicting results have been reported regarding the role of SERMs in platelet aggregation (749). Both ERα and ERβ are expressed at the membrane surface of platelets (748) (750), but the effect of hormones or analogs on platelet activation is dependent on the type of estrogen and the route of administration (751). A stimulatory role of SERMs on platelet aggregation has been described in several *in vitro* and *in vivo* studies (752) (753) (754). Tamoxifen may affect the release of intracellular Ca2+ which, in turn, would be responsible for platelet aggregation (755). The pro-aggregatory effect of tamoxifen is thought to be largely mediated by its metabolite, 4-OH tamoxifen (752). SERMs were also shown to increase platelet nitric oxide formation (756) and decrease platelet adhesion and spreading (757).

In clinical settings, tamoxifen is associated with an increased risk of venous thrombosis (635) (636), lower plasma levels of anti-thrombin and protein S1131 and increased hepatic coagulation factors (749). High venous thromboembolism incidence was reported in clinical trials examining the safety profile of several SERMs (758) (759) (760) (761): the effect appears to be further worsened by the addition of chemotherapy (254). The partial agonistic effect observed in SERMs like tamoxifen is thought to be responsible for the observed increase in thromboembolic events (762). Surgery (633) (763),

chemotherapy (764), immobilization (633), malignancy (765), central vascular access (766), smoking (767) and obesity (768) are known risk factors for thromboembolism which can further contribute to the occurrence of this outcome in breast cancer patients. Inherited hypercoagulable states such as the Factor V Leiden mutation can also further increase the risk of thromboembolism in patients treated with tamoxifen (769).

Effect of SERMs on blood pressure and coronary vascular reactivity

From a mechanistic point of view, SERMs are thought to have similar vascular tone effects to those of estrogen by antagonising various ion channels (637). Inhibition of voltage-dependent calcium channels in vascular smooth muscle cells by tamoxifen promotes the relaxation of coronary artery rings (770) (771). The vasodilatation effect of this drug can attenuate the vasoconstriction response observed in estrogen deficiency (772) (773) and lead to reduction in blood pressure (771) (774). Inhibition of protein kinase C (775) (776), reduction in mRNA expression of α1C subunit of the L-type calcium channel (777), inhibition of voltage-gated calcium current (778), and increased expression of voltage-dependent potassium channel (736) have been suggested as mechanisms by which tamoxifen may exert its vasodilation action on vascular beds. Its effect on ion channels is thought to relate to the lipophilic properties of tamoxifen which can readily insert in the lipid membrane (779) (780) (781) (782) and alter protein-lipid interactions (783) (784).

Improvement in vascular coronary reactivity following tamoxifen treatment is thought to reduce the incidence of ischemic and coronary heart diseases, especially in patients with a prior history of hypertension (771). The effect appears to be specific to the active phase of the treatment as opposed to the post-treatment period (785).

Only a few published clinical reports have explored the effect of SERMs on the blood pressure. Tamoxifen was found to have no effect on blood pressure in a randomized, double-blind placebo controlled trial that focused on cardiovascular risk factors in post-menopausal women (714). This study reported no significant changes in blood pressure measurements after repeated hospital visits. Another investigation confirmed these finding by demonstrating that tamoxifen seemed to have no effect on blood pressure, plasma renin activity, and renal sodium excretion in normotensive postmenopausal women (786). Although hypertension is not listed as a potential risk on the FDA-approved tamoxifen label, a comparative trial with anastrozole demonstrated a higher incidence of hypertension in the tamoxifen arm (787) .

SERMs and myocardial infarction

Based on a meta-analysis of clinical trials, tamoxifen is associated with a significant decrease in myocardial infarction (MI) deaths and a statistically insignificant reduction in MI

incidence (788). This drug was shown to reduce the levels of C-reactive protein (789), a known risk factor for MI (790). A Scottish study reported a lower incidence of hospital admissions for MI and ischemic heart disease in patients treated with tamoxifen, the effect being most apparent during the first year of follow-up (791). However, most reports on the cardiovascular risks associated with SERMs come from secondary analysis of clinical trials among patients at low risk of MI (792) (793) (794). More recent observational studies have failed to demonstrate any effect on the risk of MI following tamoxifen treatment in comparison to breast cancer patients not on therapy (795) (796). Since most studies have been conducted in clinical trials with stringent entry criteria regarding prior cardiovascular diseases, and in which cardiac outcomes are not the primary endpoints, the overall risk of MI for breast cancer patients on treatment remains uncertain.

Table 11: Molecular and physiological effects of Selective Estrogen Receptor Modulators on the cardiac function with their expected clinical impact

Function	Molecular or physiological effect	Expected clinical impact
Antioxidant	Reduce lipid peroxidation by scanvenging free radicals	↓atherosclerosis
	Reduce lipid peroxidation through decrease in membrane fluidity	↓atherosclerosis
Lipid levels	sterol-Δ8,7-isomerase inhibitor	↓atherosclerosis
	Acyl-CoA cholesterol acyl transferase inhibitor	↓atherosclerosis
	Reduce LDL levels	↓atherosclerosis
	Increase triglyceride levels	↑atherosclerosis
	Reduce circulating homocysteine	↓atherosclerosis
	Increase synthesis of apolipoprotein A-1	↓atherosclerosis
	Variation in HDL levels (increased, stable or decreased depending on study)	atherosclerosis
Rhythm disturbances	Inhibit cardiac potassium currents following acute exposure	QT prolongation
	Increase expression of K+ channel and K+ current density following chronic exposure	↓arrhythmia
	Drug interaction (CYP3A4, CYP2C9 and CYP2D6)	QT prolongation
Coagulation	Release of intracellular Ca2+ leading to platelet aggregation	↑thromboembolism
	Increase platelet nitric oxide formation	↓thromboembolism
	Decrease platelet adhesion and spreading	↑thromboembolism
	Low plasma levels of antithrombin III	↑thromboembolism
	Low plasma levels of protein S1131	↑thromboembolism
	Increase in coagulation factors	↑thromboembolism
Blood pressure	No effect on plasma renin activity	Blood pressure unaffected
	No effect on renal sodium excretion	Blood pressure unaffected
	Inhibition voltage-dependent Ca^{2+} channels in vascular smooth muscles	↓blood pressure
	Inhibition of protein kinase C	↓blood pressure
	Reduction mRNA expression of α1C subunit of L-type Ca^{2+} channel	↓blood pressure
	Inhibition of volage-gated Ca^{2+} current	↓blood pressure
	Increase in voltage-dependent K+ channel	↓blood pressure

Selective estrogen receptor down-regulator – Fulvestrant

Fulvestrant is another FDA-approved drug modulating its antineoplastic activity via the ER, but is different from SERMs in that it down-regulates (797) and degrades the receptor (798). This drug was developed in the search for an anti-estrogen targeting the ER without estrogenic effects.

Evidence of mild transient cardiovascular effects such as increased heart rate, panting and flushing were recorded in studies in dogs, but no effect of on QT intervals or ECG measurements have been reported in in purkinje fibers or *in vivo* (799). Activation of high conductance in Ca2+ and K+ channels in smooth muscles following fulvestrant treatment suggests a potential effect on the vasculature (800).

The cardiovascular risks associated with this therapy have not specifically been addressed in clinical trials and the information available is limited. Cerebrovascular events and deep vein thrombophlebitis have been reported, but no significant difference in the risk of thromboembolism in comparison to tamoxifen was observed (801). The Canadian product monograph for Faslodex reports slight elevations of the ST segments on electrocardiogram and sinus arrest in a canine study, but was considered to be of no significance for human safety at clinical dosage (802). No rhythmic disturbances were disclosed in clinical trial reports.

Aromatase inhibitors

In contrast to SERMs which inhibit the activity of estrogen by competitively binding to the ER, aromatase inhibitors (AIs) block the conversion of androgens to estrogen thereby reducing the levels of circulating estrogen in plasma and tissues. These inhibitors are classified as first, second or third generation inhibitors according to the chronological order of their development and are further categorized according to their mechanism of action. The steroidal analogues of androstenedione, such as exemestane, are classified as type 1 inhibitors. These inhibitors bind irreversibly to the same site as androstenedione on the aromatase molecule, whereas type 2 inhibitors such as anastrozole and letrozole are nonsteroidal in nature and bind reversibly to the heme group of the enzyme. In contrast to first and second generation inhibitors, the specificity for the aromatase enzyme of the third generation inhibitors appears to be nearly complete at clinical doses with little to no effect on basal levels of other hormones (803) (804) (805) (806). The efficacy of third-generation aromatase inhibitors was demonstrated as a first-line treatment for advanced breast carcinoma or adjuvant therapy in early disease, as well as in patients who failed to respond to tamoxifen (807) (808) (809) (810) (811).

Since the aromatase enzyme is abundantly expressed in endothelial and smooth muscle cells (812) (813) (814), it would be logical to hypothesize that AIs could affect

cardiovascular health. Surprisingly, only minimal data regarding the cardiovascular effects of AIs is available and, when information is available, the cardiovascular endpoints vary significantly from trial to trial, further complicating characterisation of the risk (815). In the last section of this overview, the cardiovascular effects attributed to AI exposure will be described and compared to the effect observed in SERMs. A summary of the molecular and physiological effects of aromatase inhibitors on cardiac function can be found in **Table *12***.

Aromatase inhibitor and oxidative stress

Reports of potential antioxidant effect of AIs on cardiovascular health are scarce in comparison to SERMs. Exemestane was shown to protect myocardiocytes against chemically generated oxidative stress resulting from exposure to *tert*-butyl hydroperoxide, 4-hydroxynonenal, and UV radiation (816). Letrozole was shown to mediate hepatoxicity through a mechanism independent of oxidative stress in female rats (817), while an increase in lipid peroxidation was detected following administration of this drug in male rats (818). More studies are required to clarify the association between AI exposure and oxidation, as well as their effects on the cardiovascular system.

Aromatase inhibitors, lipid levels and atherosclerosis

Administration of aromatase inhibitors has produced conflicting findings with respect to lipid levels and their overall effect on atherosclerosis. Treatment with various inhibitors has been reported to increase (817) (819) or to have no effect on serum lipid levels (820) (821) (822) (823) (824) (825) (826) but no significant detectable changes in plasma homocysteine (724) (824) (827) or apolipoprotein a1 (633) (828) levels have been reported. These contradictory effects may be a reflection of differences in trial design, heterogeneity of the patient populations studied, variation in previous therapy administered, differences in the specific AI administered, and the way lipid concentrations were measured in the different studies. Letrozole was shown to have no effect on total cholesterol, LDL and HDL levels in a small breast carcinoma prevention trial (829). In addition, no significant variation in serum concentrations was reported in two trials with anastrozole (822) (829) and three studies with exemestane (830) (831) (832). Exemestane was the only AI to significantly decrease HDL levels in a randomized, multi-centre trial of anastrozole, letrozole and exemestane in healthy postmenopausal women (832). Most increases in lipid levels following AI treatment were observed in trials in which patients were pre-treated, treated in combination with, or compared to patients treated with tamoxifen (724) (830) (819) (829). Findings from these studies have led to the hypothesis that the observed increase in cholesterol levels in patient treated AIs is the result of tamoxifen withdrawal, rather than a direct effect of aromatase inhibition (724). However,

one group has suggested that although most of the effect could be attributable to tamoxifen withdrawal, there are differences between patients treated with different AIs (831). This group reported an increase in LDL cholesterol following treatment with letrozole when compared to treatment with exemestane, but the latter was associated with a decrease in total HDL concentrations. Differences in androgenic effects were suggested as being responsible for this variation in the effect of AIs. Interestingly, a recent trial comparing the efficacy of exemestane versus anastrozole in postmenopausal women with early breast cancer reported a decreased in the risk of hypercholesterolemia and hypertriglyceridemia in the exemestane treatment arm (833), whereas in another study anastrozole was shown to decrease triglyceride levels in comparison to tamoxifen (820). Since controversy persists around the results from lipid analyses, monitoring of cardiovascular events as part of long-term AI trial may be necessary to shed light on the safety profile of these therapies.

Aromatase inhibitors and rhythm disturbances

No major rhythm disturbance concerns have been raised with AI exposure. The FDA-approved letrozole label discloses cases of arrhythmia leading to death in cats exposed to doses exceeding the daily recommended human dose on a mg/m^2 basis by 50 times (834). Although aromatase inhibitors are metabolised by the CYP450 enzyme, no significant

interactions leading to arrhythmia are expected at physiological relevant concentrations of anastrozole (835) or letrozole (836) treatment.

Aromatase inhibitor and thrombosis

Third generation aromatase inhibitors are associated with reduced thromboembolic risk in comparison to SERMs (807) (837) (838) (839). Thromboembolic events following anastrozole (838) (840) or letrozole (808) (841) treatment were reduced by almost two fold in comparison to rates in patients treated with tamoxifen. Patients who switched to anastrozole after tamoxifen treatment also had a reduced incidence of thrombosis and emboli compared with those who continued on tamoxifen (842). Moreover, a decreased risk in thromboembolic events was recorded following letrozole therapy or exemestane treatment (843) when compared to tamoxifen, but the risk was significantly increased in patients treated with letrozole when compared to placebo (844). Caution is warranted when attempting to draw conclusions regarding the thromboembolic risks associated with AI therapies as most of evidence available was gathered from comparative trials with tamoxifen. Since tamoxifen was reported to be associated with significant risk of thromboembolism, the absolute effect of AIs on the vasculature and clinical manifestation of the disease may be masked by differences in risk between the two drug classes. Although exemestane appears to have a stronger inhibitory effect on the

expression of protein kinase C and antithrombin III, and a stimulatory effect on Protein S1131 levels in comparison to non-steroidal AIs (845), no clinically significant difference in coagulation factors levels have been reported (846).

Aromatase inhibitors and blood pressure

Estrogen deficiency has been linked to up-regulation of aldosterone concentrations and hypertension (667) (668) (669) (670). Inhibition of the aromatase enzyme, shown to be abundant in endothelial and smooth muscle cells (814), has been associated with reduced vasodilatation in young men (847). Since AIs are potent inhibitors of estrogen synthesis, it would be logical to assume that treatment with members of this drug class would lead to increased blood pressure. Yet, interestingly, knockout mice for the expression of the aromatase enzyme demonstrate reduced diastolic and mean blood pressure (848). The reported incidence of hypertension following anastrozole treatment is 8% to 9%, whereas exemestane treatment is associated with a 5% incidence rate (240). No differences in blood pressure were reported in the MA17 trial between patients treated with letrozole or placebo (849), although a 5% to 8% increase in the incidence of hypertension has been reported in other letrozole trials (240), along with conflicting results on aldosterone levels (850) (804) (851) (852) (853). While fadrozole treatment was associated with significant sodium retention in saline-loaded rats, anastrozole had no effect on sodium or potassium

retension (852). Both anastrozole and exemestane were reported to increase blood pressure in comparison to tamoxifen (848), but these two drugs had no discernible effect on aldosterone levels (850) (854). This discrepancy between the hormone levels and detection of the outcome may be explained by differences in risk between SERMS and AIs as opposed to a direct effect of AIs. The differences observed may also be related to variation in study design or patient population.

Aromatase inhibitors, myocardial infarction and cardiac failures

In a comparative review of the cardiovascular risks associated with AIs, Nabholtz and Gligorov reported no cardiovascular safety issues with AIs in the setting of advanced breast cancer (855), recognizing the limitations in drug exposure, lack of focus on cardiovascular endpoints, and limited safety analyses. Very few trials have reported severe, high grade, cardiovascular events following AI treatment and no significant increase in C-reactive protein was detected in patients treated with first-line aromatase inhibitors (724). Letrozole was associated with a numerically higher risk of myocardial infarction in comparison to anastrozole in patients progressing on tamoxifen (856). However, no difference was observed in patients switching to anastrozole when compared to those who continued treatment with tamoxifen (842). There were also no differences in the risk of MI

in anastrozole-treated versus tamoxifen-treated patients in the ATAC trial (840) (857); this safety profile was further confirmed by the ABCSG 8/ARNO 95 trials (842) (858). However, the ATAC trial demonstrated an increased incidence of ischemic cardiovascular events following anastrozole treatment in women with pre-existing ischemic heart disease when compared to the tamoxifen arm (838) (857). A warning underscoring the potential risk in patients with pre-existing ischemic heart disease can be found on the anastrozole label (859). Of note, patients treated with letrozole as part of the BIG 1-98 trial experienced a significantly greater incidence of severe cardiac events in the form of ischemic heart diseases and cardiac failures than patients on tamoxifen (841). In this same trial, the number of cardiac deaths was doubled in the letrozole treatment arm. However, these results should be interpreted with caution since baseline cardiovascular conditions of enrolled patients were not reported (860). This increase in severe cardiovascular events and deaths was not observed in patients who switched to letrozole as opposed to placebo after 5 years of adjuvant tamoxifen (861). Although no significant difference in the overall incidence of cardiovascular events was reported between exemestane and tamoxifen (862), the incidence of myocardial infarctions was shown to be the same (844) (862) or more frequent following exemestane treatment (843) (844) (855). Although an observational study from Ligibel et al reported no significant risk in MI following AI or tamoxifen therapy (795), Seruga et al demonstrated in a 2014 study a relation between AI and coronary disease (634). A similar increase in cardiovascular events following AI exposure was shown in meta-analyses of clinical trials (863) (864).

Table 12: Molecular and physiological effects of aromatase inhibitors on the cardiac function

Function	Molecular or physiological effect
Antioxidant	Exemestane: protection against oxidative stress
	Letrozole - ↑ in lipid peroxidation in male rats
Lipid levels	Decreased to stable levels of HDL
	Stable levels of LDL and total cholesterol
Coagulation	No discernable changes on fibrinogen levels
	Effect reported attributable to tamoxifen withdrawal
Blood pressure	Conflicting results on aldosterone levels - Fadrozole: retention - Anastrozole: no effect
Blood flow	Increased incidence of ischemic cardiovascular events and coronay artery diseases

Conclusion

Large studies have demonstrated the advantages of estrogen-targeted therapies in treatment of breast cancer with respect to disease free survival, risk of recurrence, and reduction in lethal distant metastatic events (810) (841) (843). Considering this marked improvement in efficacy and increased survival post-breast cancer diagnosis, the risk of cardiovascular events and other drug-related outcomes needs to be taken into consideration in therapy selection.

One of the most widely employed adjuvant breast cancer therapy, tamoxifen, has paradoxic properties regarding cardiovascular risks principally owing to its dual agonist and antagonist estrogenic effects. Although this drug was reported to have a positive effect on lipid profiles (844) (865) (866) (867) (868), its use is associated with a significance increase in the incidence of thromboembolism and ischemic stroke (869). Since AIs lack such estrogenic agonist effects, no similar contradiction surrounds the use of these drugs. However, evidence from large comparative clinical trials with tamoxifen may mask the cardiovascular effects of AIs to a certain extent. In such trials, the cardiovascular responses attributable to tamoxifen may preclude a comprehensive understanding of the relative risk associated with AIs.

Meta-analyses of clinical trials (863) (864) and a recent observational study (634) reported an increase in cardiovascular events following AI exposure, but the use of AIs in large randomized trials was not associated with an overt increase in cardiovascular risks and only a slight beneficial effect on thromboembolic events was identified (807) (808) (837) (870). Nonetheless, it should be recognised that these studies were limited in duration of exposure and that these trial were not designed for the prospective evaluation of cardiac safety. The patient populations recruited were often at low baseline risk of adverse cardiovascular events. The reported cardiotoxicity may underestimate the actual risk profile associated with long-term use. Due to the slight increase in the rate of occurrence of certain cardiovascular outcomes, particularly when tamoxifen is used as a comparator, additional follow-up studies are required to clarify this issue. Furthermore, different drug combinations must be assessed for their synergistic cardiotoxic potential.

Meanwhile, practitioners responsible for the care of these patients must make treatment decisions based on the available data. Although a formal screening algorithm or monitoring requirements are lacking, lifestyle modifications may be employed to reduce estrogen-targeted therapy-related cardiotoxicity. Increased physical activity and reduction in body mass index have been shown to improve the overall cardiovascular health of breast cancer patients on adjuvant endocrine therapies (620). In terms of prophylaxis, co-administration of coenzyme Q10 supplements along with tamoxifen has been shown to alleviate the increase in triglyceride levels associated with SERMs (871). A number of

different considerations are relevant in making treatment decisions. Both risks and benefits should be assessed before a decision is made regarding the best treatment option for breast cancer patients in order to maximize tumor response while minimizing possible cardiac damage. Taken together, this suggests that an interdisciplinary approach between oncology and cardiology is required to optimize long-term patient outcomes.

Chapter 4

Cardiovascular risks associated with estrogen-targeted therapy in post-menopausal women with breast cancer

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Description and statement of contributions of collaborators and co-authors

This manuscript presents the results of a pharmacoepidemiological study of the cardiovascular risks associated with estrogen targeted therapies in post-menopausal women with breast cancer. Specifically, a case-control study was used to investigate the potential risk of myocardial infarction and heart failure following exposure to selective-estrogen receptor modulators and down-regulators as well as aromatase inhibitors. The study accounts for the potential cofounding effects of a variety of socio-demographic factors, disease characteristics, concomitant therapies, and comorbidities.

S. Hamel formulated the hypothesis for this study and performed the statistical analysis, SAS coding and literature search required for this manuscript with guidance from Dr. Krewski. S. Hamel created all tables presented and wrote the text with review and editing from Dr. D. Krewski, Dr. A. Krantis, Dr. D. McNair, Dr. D. Mattison, and Dr. N. Birkett. All contributors were involved in the evaluation and interpretation of the study findings.

Abstract

Purpose

The purpose of this paper is to investigate the cardiovascular risks associated with estrogen-targeted therapies (ETs) in a heterogeneous population of post-menopausal female breast cancer patients, and to compare the risk profile of selective estrogen receptor modulators and down-regulators (SERM/DRs) to that of aromatase inhibitors (AIs).

Methods

Data from the Cerner Corporation's HealthFacts™ Datawarehouse was used to conduct a nested case-control study by sampling post-menopausal women diagnosed with breast cancer between January 2000 and June 2013 who were treated by at least one of the following modalities: breast surgery or at least one recorded encounter with a cancer therapy following breast cancer diagnosis. Cases of myocardial infarction (MI) or heart failure (HF) were matched on age (±2years) and date of breast cancer diagnosis (±1year) to 4 randomly selected breast cancer patients with no history of either cardiovascular events of interest as of the index date. Conditional logistic regression was used to estimate both crude and adjusted odds ratios (ORs), along with 95% confidence intervals for the risk associated with each cardiovascular outcome following exposure to AIs or SERM/DRs.

Results

A total of 11,952 breast cancer patients with a median age of 66 years met the inclusion criteria for this study. A significant increase in the risk of HF was associated with the use of ETs (adjusted odd ratio (aOR)= 1.386, 95% confidence interval: 1.105, 1.739) and, more specifically, AIs (aOR= 1.417, 95% CI: 1.102, 1.821), in comparison with breast cancer patients not receiving these therapies, after adjustment for surgery, presence of secondary tumor(s), and administration of proton pump inhibitors. The risk of HF was not significantly increased following exposure to SERM/DRs (aOR= 1.170, 95% CI: 0.861, 1.590), following adjustment for the same covariates. The risk of MI was not significantly increased following exposure to any of estrogen-targeted therapies after adjustment for potential confounders.

Conclusion

These results suggest an increase in the risk of HF due to the use of AIs, but not SERM/DRs. None of the estrogen-targeted therapies were associated with a statistically significant increase in MI risk.

Introduction

Most breast cancer (BC) cases are diagnosed in post-menopausal women (872), the majority of whom exhibit at least one risk factor for cardiovascular diseases (171) (873). Although estrogen-targeted therapies (ETs) are routinely prescribed as adjuvant treatments in post-menopausal women with hormone-dependent BC, the cardiovascular effects of ETs remain controversial. Notwithstanding evidence of a potential cardioprotective effect of tamoxifen (788) (789) (791), most reports on the cardiovascular effect of ETs are based on secondary analyses of clinical trial data involving patients at low risk of cardiovascular diseases (792) (793) (794). Two trials (874) (875) and one observational study (796) failed to demonstrate any effect of tamoxifen treatment on the cardiovascular system.

Although a clinical trial review (855) reported no association between aromatase inhibitors (AIs) and cardiovascular events, evidence from large comparative clinical trials with tamoxifen may mask the cardiovascular effects of AIs and preclude comprehensive understanding of the relative risk associated with AIs. A 2014 study by Seruga *et al* showed an association between AIs and coronary heart diseases (634) and meta-analyses of clinical trials have also suggested an increased risk of adverse cardiovascular events following AI exposure (864) (863).

Since most previous studies have been based on data from clinical trials in which cardiac outcomes are not the primary endpoints and with stringent entry criteria regarding prior cardiovascular diseases, the overall cardiovascular risk for BC patients receiving endocrine therapy remains uncertain. The purpose of this study is to estimate the potential cardiovascular disease risks associated with endocrine treatment to better characterize the safety profile of these drugs in a heterogeneous population of BC patients under real-world conditions of use.

Methods

Source of data

This study was based on anonymized data abstracted from electronic health records included in the Cerner HealthFacts™ Datawarehouse. At the time of this analysis, this large database was composed of encrypted time-stamped information on distinct inpatient admissions as well as emergency department and outpatient visits collected from 349 hospitals and clinics throughout the United States. Episodes of care are linked to individual patients by means of unique identifiers to permit the assessment of clinical progression of disease and sequential therapeutic administration. Accessed information included patient demographics (age, gender, and marital status), treating center characteristics (census region, number of beds), prescribed and dispensed medications (orders, dispensing events, billing and insurance plan, National Drug Code number, quantity and date of administration), and medical diagnoses and procedures (ICD-9-CM codes).

Study population and eligibility criteria

We identified all women with a diagnosis of BC (ICD-9-CM 174, 238.3, 239.3) from January 2000 to June 2013 who were treated by at least one of the following modalities: either by breast surgery and/or by a cancer therapy. These therapies included: all alkylating

agents, antimetabolites, anti-tumor antibiotics, topoisomerase inhibitors, anti-mitotic agents, ETs, small molecule inhibitors, monoclonal antibodies, immunomodulators and other hormonal agents approved by the FDA as a cancer therapy at the time of the study. Patients treated with these antineoplastic agents prior to their first recorded diagnosis of BC were excluded to ensure that the initial diagnosis was captured. At least six months of recorded care prior to the first BC diagnosis was required for patients to be included in this study, because those with shorter follow-up were considered less likely to have potential comorbidities fully recorded. Pre-menopausal women were excluded from the analysis as most of these drugs are indicated for use in a post-menopausal setting. An attained age of 50 years was used as an indicator of post-menopausal status, as described elsewhere. (876) (877) (878).

Case-Control analysis

A nested case-control study was conducted to assess the risks of myocardial infarction (MI) and heart failure (HF) based on exposure to ETs, including SERM/DRs and AIs. All cases were identified from the study population and classified into two categories (MI or HF) based on ICD-9-CM code diagnoses (410, 410.x, 410.xx and 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.13, 404.91, 404.93, 428, 428.x, 428.xx, respectively). Using the same study population, 4 female BC controls with no history of MI or HF were matched to each case on age at first BC diagnosis (±2 years) and date of first BC diagnosis

(±1 year). Potential controls had no record of death prior to the index date, defined as the earliest recorded MI or HF diagnosis for each case. As a sensitivity analysis, a second group of controls was selected based on the same matching criteria, but controls also had to have had at least one encounter after the index date to confirm that the patient was still alive. Patients selected as controls who were later diagnosed with MI or HF were also included as cases in the analysis.

Identification of endocrine therapies under study and drug exposure

Any ETs approved by the FDA at the time of the study to treat BC were included in the analysis. ETs were classified as SERM/DRs or AIs based on their mechanism of action. The specific drugs included in each category are summarized in **Table *13***. Drug exposure was determined from pharmacy orders and dispensing events using time and date stamped National Drug Code numbers. Cases of MI or HF had to have had at least one prescription before the occurrence of the cardiovascular event being investigated to be considered exposed.

Table 13: Estrogen-targeted therapies approved by the FDA for the treatment of breast cancer at the time of the study.

Categories	Drugs
Selective estrogen receptor modulator or downregulator	Fulvestrant, Tamoxifen, Toremifene
Aromatase inhibitors	Anastrozole, Letrozole, Exemestane

Statistical analysis

The risk of MI and HF associated with exposure to ETs was assessed and stratified by drug category (SERM/DRs and AIs). The crude and adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) were estimated using conditional logistic regression as implemented in SAS (Version 9.2, SAS Institute, Cary, NC). The risk of MI and HF associated with each of 22 variables listed in **Table *14***, including several known risk factors for cardiovascular disease, were evaluated using univariate logistic regression. These variables were also considered as potential confounders of the association between ETs and cardiovascular disease: if the inclusion of any of these potential confounders changed the estimate of risk associated with ETs by 10% or more, they were retained as covariates in the final multivariate logistic regression model used to estimate the risk of MI and HF following exposure to ETs, adjusting for potential confounders. Socio-demographic factors including age, ethnicity, marital status, drug coverage, census region and hospital bed size were ascertained at the time of initial BC diagnosis. Information on the region of the breast implicated in the malignancy was also collected at the time of first BC diagnosis, whereas lymph node involvement and secondary cancers were considered at or after that date. ICD-9 codes (196, 196.x and 197, 197.x, 198, 198.x, 209.x, respectively) were used to assess the extent of disease, since pathological reports were not available to determine tumor stage. Because both radiotherapy (624) (879) and treatment with chemotherapies (880) can potentially increase the risk of cardiovascular disease, treatments with ionizing radiation, alkylating agents, antimetabolites, anti-tumor antibiotics, topoisomerase inhibitors, anti-

mitotic agents, small molecule inhibitors, monoclonal antibodies, immunomodulators and other hormonal agents were considered as covariates for inclusion in the multivariate logistic regression analysis. Although cardiac complications are infrequently reported following mastectomy (630), breast surgery was considered as a possible confounder. Ever use of hormone replacement therapy (HRT), proton pump inhibitors (PPIs) or diagnosis of hypertension, hyperlipidemia and diabetes were also investigated for their potential confounding effect, given previously described associations between PPIs (881) or co-morbidities (882) (883) (884) and the cardiovascular outcomes of interest.

Table 14: Variables assessed for their potential confounding effect on the association between the use of estrogen-targeted therapies in the treatment of breast cancer and cardiovascular disease risk

Categories	Variables
Demographic	Ethnicity, marital status, census region
Treatment centre	Urban vs rural region, number of beds
Disease characteristics	Tumor site, lymph node involvement, secondary tumor
Cancer treatment	Surgery, alkylating agents, anti-metabolites, anti-cancer antibiotics, anti-mitotic agents, hormone therapies, immunotherapies, radiotherapy, small molecule inhibitors
Concomitant therapies	Hormone replacement therapy, proton pump inhibitors
Comorbidities	Hypertension, diabetes, hyperlipidemia

Any variable changing the estimate of risk by 10% or more were kept in the final adjusted model.

Results

Patient population

A total of 11,952 women with a median age of 66 (range 50-90) years met the inclusion criteria for this study. All subjects over 89 years of age were assigned an age of 90 years for de-identification purposes. Although the database contained information on 74,050 post-menopausal female BC patients, 32,500 patients were excluded due to lack of at least 6 months of recorded care prior to the index date; 28,752 were excluded because they did not meet the criteria for recorded treatment after BC diagnosis; and 846 were excluded due to a history of cardiovascular disease prior to the initial diagnosis of BC. Within this study population, 184 and 839 women were diagnosed with MI and HF, respectively. All cases were matched to 4 controls based on age and time of BC diagnosis, with no cases lost to matching.

Subject characteristics

Socio-demographic characteristics of the cases and controls included in this study are presented in **Table *15***. Because cases and controls were matched on age, the age distribution of the case and control series is similar, with most patients being over 70 years of age. Caucasians patients were over-represented, accounting for 90% of the study population; nonetheless, non-Caucasians did not demonstrate a significant difference in

risk of either MI (OR = 0.947, 95% CI: 0.533, 1.647) or HF (OR = 1.061, 95% CI: 0.829, 1.359), as compared to Caucasians. Marital status and payer class were unknown for a large proportion of subjects. These two socio-demographic factors were not significant predictors of the risk of MI or HF. Although patients with prescription drug coverage other than Medicare demonstrated significant decreased risk of HF relative to those covered by Medicare, these results should be interpreted with caution as payer class was unknown for more than 45% of cases. A total of 206 out of the 349 treatment centres providing information to HealthFacts^{TM} contributed data to this analysis. Treatment centres in the Northeast region were associated with a higher risk of MI and HF. Although only 20.6% (72 out of 349) of treatment centres were located in the Northeastern region, this census region was over-represented, with more than half of patients being treated in this region. Medium size treatment centres were associated with slightly reduced risk of diagnosis of MI and HF than larger centres (500+ beds) and smaller institutions (1-99 beds).

Table 15: Demographic, treating centre and insurance coverage and drug characteristics of study post-menopausal breast cancer patients, and the associated risk of myocardial infarction (MI) and heart failure (HF).

Variables	Variable categories	MI Cases (n=184) n (%)	MI Controls (n=736) n (%)	MI OR	MI CI (95%)	HF Cases (n=839) n (%)	HF Controls (n=3356) n (%)	HF OR	HF CI (95%)
Age	50-59 (ref)	20 (10.9%)	83 (11.3%)	●	●	111 (13.2%)	436 (13.0%)	●	●
	60-69	38 (20.6%)	155 (21.1%)	●	●	183 (21.8%)	756 (22.5%)	●	●
	70-79	69 (37.5%)	266 (36.1%)	●	●	283 (33.7%)	1125 (33.5%)	●	●
	80+	57 (31.0%)	232 (31.5%)	●	●	262 (31.2%)	1039 (31.0%)	●	●
Ethnicity	Caucasian (ref)	166 (90.2%)	652 (88.6%)	Ref	Ref	745 (88.8%)	2961 (88.2%)	Ref	Ref
	Other	17 (9.2%)	70 (9.5%)	0.937	0.533, 1.647	92 (11.0%)	346 (10.3%)	1.061	0.829, 1.359
	Unknown *	1 (0.6%)	14 (1.9%)	*	*	2 (0.2%)	49 (1.5%)	*	*
Marital status	Married (ref)	38 (20.7%)	231 (31.4%)	Ref	Ref	208 (24.8%)	1100 (32.8%)	Ref	Ref
	Other	58 (31.5%)	296 (40.2%)	1.346	0.805, 2.250	317 (37.8%)	1318 (39.3%)	1.230	0.991, 1.527
	Unknown *	88 (47.8%)	209 (28.4%)	*	*	314 (37.4%)	938 (27.9%)	*	*
Prescription	Medicare (ref)	77 (41.9%)	326 (44.3%)	Ref	Ref	327 (39.0%)	1461 (43.5%)	Ref	Ref
drug converage	Others	31 (16.8%)	162 (22.0%)	0.706	0.384, 1.297	132 (15.7%)	668 (19.9%)	0.695	0.507, 0.953
	Unknown *	76 (41.3%)	248 (33.7%)	*	*	380 (45.3%)	1227 (36.6%)	*	*
Census region	Northeast	117 (63.6%)	373 (50.7%)	Ref	Ref	450 (53.6%)	1605 (47.8%)	Ref	Ref
	Midwest	29 (15.8%)	156 (21.2%)	0.577	0.365, 0.910	199 (23.7%)	704 (21.0%)	1.011	0.836, 1.222
	South	27 (14.7%)	132 (17.9%)	0.637	0.398, 1.019	145 (17.3%)	640 (19.1%)	0.788	0.634, 0.979
	West	11 (6.0%)	75 (10.2%)	0.448	0.228, 0.878	45 (5.4%)	407 (12.1%)	0.384	0.276, 0.533
Urban region	Yes	184 (100.0%)	732 (99.5%)	Ref	Ref	837 (99.8%)	3340 (99.5%)	Ref	Ref
	No	0 (0.0%)	4 (0.5%)	◊	◊	2 (0.02%)	16 (0.05%)	◊	◊
Bed size	500+	62 (33.7%)	180 (24.5%)	Ref	Ref	240 (28.6%)	726 (21.6%)	Ref	Ref
	300-499	39 (21.2%)	191 (25.9%)	0.593	0.377, 0.934	242 (28.8%)	958 (28.5%)	0.759	0.618, 0.933
	200-299	49 (26.6%)	231 (31.4%)	0.607	0.395, 0.931	218 (26.0%)	1036 (30.9%)	0.627	0.508, 0.774
	100-199	13 (7.1%)	76 (10.3%)	0.493	0.256, 0.950	63 (7.5%)	339 (10.1%)	0.556	0.409, 0.756
	1-99	21 (11.4%)	58 (7.9%)	1.052	0.587, 1.886	76 (9.1%)	297 (8.9%)	0.769	0.572, 1.032

*Unknowns not included in univariate logistic regression analysis
●: Odds ratio not shown because cases and controls were matched on age
Ref: reference
◊: Logistic regression model did not converge because of small number of patients

A comparison of the disease and treatment characteristics between cases and controls is given in **Table *16***. When specified, the upper-outer quadrant was the most frequent site of initial breast cancer diagnosis (21.2% for cases, 22.8% for controls), although the region of the breast affected was not a significant predictor of cardiovascular disease risk. In patient with more advanced disease, lymph node involvement was not associated with an increase in risk of MI (OR=0.924, 95% CI: 0.577, 1.479) or HF (OR=1.209, 95% CI: 0.976, 1.496); however, the diagnosis of a secondary tumor was associated with an

elevated risk of both MI and HF. Treatment with antineoplastic therapies such as chemotherapies, targeted agents, hormone therapies and immunotherapies was associated with both cardiovascular outcomes, whereas no such association was observed with radiation treatment. Patients who underwent breast surgery (mastectomy, partial mastectomy, or excision) were less likely to be diagnosed with MI or HF than those who did not.

Table 16: Disease and treatment characteristics of study post-menopausal breast cancer patients, and the associated risk of myocardial infarction (MI) and heart failure (HF).

		MI				HF			
Variables	**Variable categories**	**Cases (n=184) n (%)**	**Controls (n=736) n (%)**	**OR**	**CI (95%)**	**Cases (n=839) n (%)**	**Controls (n=3356) n (%)**	**OR**	**CI (95%)**
Region of breast	Upper-outer quadrant	39 (21.2%)	168 (22.8%)	Ref	Ref	202 (24.1%)	721 (21.5%)	Ref	Ref
	Central portion	6 (3.2%)	22 (3.0%)	1.199	0.457, 3.144	46 (5.5%)	132 (3.9%)	1.236	0.855, 1.787
	Lower-outer quadrant	9 (4.9%)	31 (4.2%)	1.272	0.552, 2.928	40 (4.8%)	141 (4.2%)	1.006	0.683, 1.480
	Upper-inner quadrant	7 (3.8%)	32 (4.3%)	0.953	0.392, 2.318	28 (3.3%)	141 (4.2%)	0.703	0.454, 1.088
	Nipple	4 (2.2%)	19 (2.6%)	0.912	0.295, 2.824	23 (2.7%)	86 (2.6%)	0.941	0.577, 1.534
	Lower-inner quadrant	7 (3.8%)	19 (2.6%)	1.614	0.633, 4.117	32 (3.8%)	114 (3.4%)	1.002	0.663, 1.523
	Axillary	0 (0.0%)	7 (1.0%)	◊	◊	5 (0.6%)	17 (0.5%)	1.046	0.382, 2.865
	Unspecified	112 (60.9%)	438 (59.5%)	1.111	0.736, 1.678	463 (55.2%)	2004 (59.7%)	0.818	0.677, 0.987
Lymph node	No	160 (87.0%)	633 (86.0%)	Ref	Ref	707 (84.3%)	2905 (86.6%)	Ref	Ref
involvement	Yes	24 (13.0%)	103 (14.0%)	0.924	0.577, 1.479	132 (15.7%)	451 (13.4%)	1.209	0.976, 1.496
Secondary cancer	No	157 (85.3%)	689 (93.6%)	Ref	Ref	713 (85.0%)	3130 (93.3%)	Ref	Ref
	Yes	27 (14.7%)	47 (6.8%)	2.659	1.575, 4.488	126 (15.0%)	226 (6.7%)	2.454	1.942, 3.102
Surgery	No	66 (35.9%)	161 (21.9%)	Ref	Ref	328 (39.1%)	775 (23.1%)	Ref	Ref
	Yes	118 (64.1%)	575 (78.1%)	0.516	0.367, 0.725	511 (60.9%)	2581 (76.9%)	0.462	0.393, 0.543
Anti-neoplastic agents	No	128 (69.6%)	588 (79.9%)	Ref	Ref	581 (69.2%)	2759 (82.2%)	Ref	Ref
	Yes	56 (30.4%)	148 (20.1%)	1.750	1.213, 2.524	258 (30.8%)	597 (17.8%)	2.107	1.767, 2.511
Radiotherapy	No	171 (92.9%)	667 (90.6%)	Ref	Ref	772 (92.0%)	3040 (90.6%)	Ref	Ref
	Yes	13 (7.1%)	69 (9.4%)	0.721	0.382, 1.359	67 (8.0%)	316 (9.4%)	0.825	0.621, 1.096

Ref: reference
◊: Logistic regression model did not converge because of small number of patients

Although rates of hypertension, hyperlipidemia and diabetes diagnoses were similar between cases and controls at the time of their initial breast cancer diagnosis, the effects of these comorbidities on the risk of developing the cardiovascular outcomes of interest at

the index date are given in ***Table 17***. Known cardiovascular risk factors such as diagnosis of hypertension, hyperlipidemia/artheriosclerosis and diabetes all demonstrated increased risks of both MI and HF. Only a negligible percentage of cases and controls were receiving HRT (≤0.5%), whereas PPIs were commonly prescribed and associated with increased risk in MI (OR=1.661, 95% CI: 1.156, 2.387) and HF (OR= 2.092, 95% CI: 1.763, 2.481).

Table 17: Exposure to other therapies and presence of comorbidities of study post-menopausal breast cancer patients, and the associated risk of myocardial infarction (MI) and heart failure (HF).

Variables	Exposure	MI				HF			
		Cases (n=184) n (%)	Controls (n=736) n (%)	OR	CI (95%)	Cases (n=839) n (%)	Controls (n=3356) n (%)	OR	CI (95%)
HRT	No	183 (9.5%)	736 (100.0%)	Ref	Ref	838 (99.9%)	3352 (99.9%)	Ref	Ref
	Yes	1 (0.5%)	0 (0.0%)	◊	◊	1 (0.1%)	4 (0.1%)	◊	◊
PPI	No	125 (67.9%)	571 (77.6%)	Ref	Ref	556 (66.3%)	2685 (80.0%)	Ref	Ref
	Yes	59 (32.1%)	165 (22.4%)	1.661	1.156, 2.387	283 (33.7%)	671 (20.0%)	2.092	1.763, 2.481
Hypertension	No	30 (16.3%)	259 (35.2%)	Ref	Ref	169 (20.1%)	1272 (37.9%)	Ref	Ref
	Yes	154 (83.7%)	477 (64.8%)	2.866	1.873, 4.386	670 (79.9%)	2084 (62.1%)	2.615	2.159, 3.168
Hyperlipidemia/atheriosclerosis	No	36 (19.6%)	341 (46.3%)	Ref	Ref	274 (32.7%)	1657 (49.4%)	Ref	Ref
	Yes	148 (80.4%)	395 (53.7%)	3.668	2.451, 5.487	565 (67.3%)	1699 (50.6%)	2.117	1.792, 2.501
Diabetes	No	103 (56.0%)	554 (75.3%)	Ref	Ref	489 (58.3%)	2617 (78.0%)	Ref	Ref
	Yes	81 (44.0%)	182 (24.7%)	2.335	1.675, 3.256	350 (41.7%)	739 (22.0%)	2.514	2.142, 2.950

HRT: Hormone replacement therapy
PPI: Proton pump inhibitor
Ref: reference
◊: Logistic regression model did not converge because of small number of patients

ETs and risk of MI

Results in **Table *18*** indicate that although exposure ETs appeared to be associated with an increase in the crude risk of MI (OR=1.867, 95% CI: 1.267, 2.753), no significant

increase in risk was detected after adjustment for breast surgery, PPI exposure and presence of secondary tumor (OR=1.199, 95% CI: 0.743, 1.934). Similarly, no significant increase in the risk of MI was detected following exposure to SERM/DRs and AIs after adjustment for the same covariates. (Although hypertension and marital status were also flagged for potential confounders of the association between SERM/DRs and MI, according to the 10% change in OR rule, the risk of MI associated with SERM/DRs was similar regardless of whether or not hypertension and marital status were included in the model. In the interests of simplicity, estimates of the risk of MI associated with both AIs and SERM/DRS were therefore adjusted for a common set of three covariates, surgery, secondary tumor and PPIs.)

ETs and risk of HF

The crude risk of HF following exposure to ETs was numerically higher than the risk of MI (OR=2.401, 95% CI: 1.986, 2.903). The risk estimates for HF remained statistically significant for exposure to ETs (aOR= 1.386, 95% CI: 1.105, 1.739) and AIs (aOR= 1.417, 95% CI: 1.102, 1.821) after adjustment for prior breast surgery, presence of a secondary cancer and exposure to PPIs. The risk of HF following SERM/DRs exposure was no longer significantly increased after adjustment for the same confounders (aOR= 1.170, 95% CI: 0.861, 1.590).

Table 18: Crude (OR) and adjusted (aOR) odds ratios for myocardial infarction (MI) and heart failure (HF) following exposure to estrogen-targeted therapies (ETs)

Categories	Subcategories	MI				HF			
		OR	95% CI	aOR	95% CI	OR	95% CI	aOR	95% CI
ETs		1.867	1.267, 2.753	1.199	0.743, 1.934	2.401	1.986, 2.903	1.386	1.105, 1.739
	SERM/DRs	1.762	0.977, 3.178	1.145	0.604, 2.170	1.919	1.443, 2.552	1.170	0.861, 1.590
	AIs	1.761	1.124, 2.759	1.16	0.698, 1.929	2.441	1.951, 3.054	1.417	1.102, 1.821

aOR adjusted for: surgery, secondary cancer, proton pump inhibitors

Discussion

In the present study of female breast cancer patients treated with estrogen-targeted therapies, we found no increase in the risk of MI but a significant increase in the risk of HF following exposure to aromatase inhibitors (aOR= 1.417, 95% CI: 1.102, 1.821), even after consideration of the potential confounding effects of 22 covariates reflecting socio-demographic, comorbidities, disease, and treatment characteristics. SERM/DRs were not associated an increased risk of HF (aOR 1.170, 95% CI: 0.761, 1,590). The overall risk for ETs was also significantly increased (aOR=1.386, 95% CI: 1.105, 1.739). These results are based on the assumption that all subjects remained under follow-up, in the absence of evidence that they were deceased. In a sensitivity analysis requiring at least one encounter after the case index date as evidence of continued follow-up, the overall risk of ETs remained significant (aOR = 1.291, 95% CI 1.029, 1.620), although slightly reduced, after adjustment for the same covariates. The risk of HF associated with AIs was also reduced (aOR = 1.232, 95% CI 0.961, 1.580), but remained numerically elevated, and close to statistical significance. The risk of HF associated with SERM/DRs in this sensitivity analysis (aOR = 1.211, 95% CI 0.895, 1.640) was similar to that in the baseline analysis.

In interpreting the results of the baseline and sensitivity analyses presented here, we would tend to give more weight to the baseline results, based on the expectation that breast cancer patients in the present cohort would, for the most part, remain within the

same health system following a diagnosis of breast cancer, and hence continue to be followed-up. While it is possible that some patients who died outside of the health care institution in which they were being treated may have been lost to follow-up, the consistency between the baseline and sensitivity analyses is reassuring.

These results are consistent with two meta-analyses (864) (863) and a recent observational study (634) that all suggested an increased rate of serious cardiac events in patients treated with AIs. Cardiac concerns are listed in Precautions and Warnings section of the prescribing information for Arimidex (anastrozole) based on comparative trials of tamoxifen exposure. While AIs were associated with a higher risk of HF in our study, no such increase in the risk of MI was seen, a finding that is consistent with results of a study from Ligibel *et al* (795). These observations suggest that coronary diseases, changes in lipid levels, and formation of arteriosclerotic plaque may not be the main mechanisms by which AIs modulate cardiovascular disease risk. Cardioprotective properties have been attributed to tamoxifen because of its beneficial effect on circulating lipids both *in vivo* and in clinical settings (712) (789) (712) (830). Such cardioprotective mechanisms have not been established following exposure to AIs. Many studies reporting changes in lipid levels following exposure to AIs involved patients pre-treated with tamoxifen, treated in combination with tamoxifen, or compared to patients treated with tamoxifen (724) (885). This has led to the hypothesis that the observed increase in cholesterol levels in patients treated with AIs is the result of tamoxifen withdrawal, rather than a direct effect of

aromatase inhibition (724). Exposure to AIs is generally associated with minimal changes in lipid profiles and is likely to be of little relevance in BC patients (886) (887) (811). Studies in aromatase knockout mice have shown that the absence of estrogen production can lead to cardiac hypertrophy and impaired cardiac function, which sensitizes the heart to pathological insults through the up-regulation of hypertrophic pathways (660). Moreover, estrogen deficiency has also been linked to the modulation of the renin-angiotensin-aldosterone system (888), leading to high aldosterone concentrations in serum (667) (668) (669), sodium and water retention, increased blood volume and elevated blood pressure. The increase in HF observed in our study following exposure to aromatase inhibitors could be linked to the activation of hypertrophic mechanisms as a result of estrogen deprivation.

Comorbidities such as hypertension (889) (890), hyperlipidemia/artheriosclerosis (891) and diabetes (892) are common in BC patients, and are important prognostic factors in their survival. In accordance with these observations, we have reported high levels of hypertension, hyperlipidemia/arteriosclerosis and diabetes among both cases and controls, which underscore the need to investigate the safety profiles of new treatments in BC populations at high risk of cardiovascular disease, especially given that many trials exclude high risk patients and are not designed to detect cardiovascular outcomes.

Although the incidence of breast cancer is higher in Caucasian patients than other ethnic populations (893), these patients are overrepresented in the present study. According to the 2010 US Census, 63.7% of the total US population was of Caucasian origin (894). This overrepresentation may explain why ethnicity had no significant influence on the risk of cardiovascular diseases, as previously reported in the literature (895). The high proportion of patients with unknown marital status may also contribute the observed lack of association between marital status and the cardiovascular outcomes in the present study, an observation which differs from previous reports (896) (897). Despite the incomplete reporting of marital status, its potential confounding effect on the risk of MI and HF associated with ETs was assessed. For consistency, marital status was not retained as a covariate in the multivariate logistic regression analysis: this covariate changed the risk estimate by slightly more than 10% only for the risk of MI associated with SERM/DRs, leading to a minimal increase in the adjusted OR (aOR=1.339, 95% CI: 0.6.92, 2.591). While various statistical methods have been proposed to address missing data (898), the exclusion of patients with missing marital status would have significantly reduced the size of our patient population. We have run a sensitivity analysis to look at the effect of removing patients with unknown marital status from the multivariate model for the risk of MI associated with SERM/DRs. The ORs for the analyses including (aOR= 1.145, 95% CI: 0.604, 2.170) and excluding (aOR=1.289, 95% CI: 0.659, 2.519) patients with unknown marital status were very similar, suggesting minimal confounding effect of marital status on the risk of MI.

A previous report showed appreciable geographic variation in cardiovascular disease in the US (899). Our study showed a modest association between treatment in the Northeast and diagnosis of MI and HF. The Centers for Disease Control and Prevention (CDC) reported a higher proportion of age-adjusted mortality from heart disease in white females located in the north/central eastern regions of the US from 1982 and 1992 (900). However, as the Northeastern region represented 19% of the US population in the 2000 census (901), this region is overrepresented in this study, with about half of the patients being in this region.

The disproportionate diagnosis of breast cancer in the upper-outer quadrant observed our study is in line with previous reports (902) (903). We found that about 11% of patients developed secondary tumors during the course of the study and that diagnosis of a secondary tumor was associated with an increase in the risk of both MI (OR= 2.659, 95% CI: 1.575, 4.488) and HF (OR=2.454, 95% CI: 1.942, 3.102). Since approximately one in every 20 patients is expected to develop a secondary tumor within 10 years of breast cancer diagnosis (904) (905), patients in our study generally presented with a more advanced disease state than the general breast cancer population. The increase in cardiovascular risks associated with the diagnosis of secondary tumor and inclusion of this diagnosis as covariate in most adjusted multivariate logistic regression analyses could be attributable to more aggressive treatment of metastatic disease.

As expected from previous reports on the cardiovascular disease risks associated with antineoplastic therapies (555) (906), patients treated with such agents were at higher risk of developing MI and HF. Among the small number of patients treated with radiotherapy, this treatment modality was not associated with higher risk of MI and HF, although a correlation between breast radiation and cardiovascular outcomes has been previously demonstrated (624). However, cardiac exposure to ionizing radiation from breast radiotherapy has decreased during the last decades (625) and the lifetime risk of major coronary events in breast cancer patients now in the range of 0.05% to 3.5% (626).

Surgery was associated with a significant decrease in both the risk of MI and HF in univariate logistic regression analysis used to estimate unadjusted ORs. The inclusion of surgery in all multivariate logistic regression models that adjusted for the effects of potential confounders tended to attenuate the estimates of risk for both MI and HF associated with ETs, with adjusted ORs being closer to unity than the unadjusted ORs. As breast surgeries are considered low-risk procedures (≤1%) for cardiovascular events (907) (908), the apparent protective effect of surgery on the risk of MI and HF found in this study is an unexpected observation. Because primary endocrine therapy is not usually recommended for post-menopausal women with estrogen receptor positive tumors who are fit for surgery, unless refused by the patient (909), including surgery as a potential confounder in the multivariate logistic regression analyses could attenuate the estimates of

risk associated with ETs because these two treatment modalities are usually used in combination. If surgery is removed from the adjusted multivariate analysis, the estimate of risk of HF associated with ETs is increased (aOR= 1.777, 95% CI: 1.445, 2.185). Yet, this does not explain the reduced risk of cardiovascular disease associated with breast surgery in the univariate logistic regression model. Despite studies showing some survival advantage for primary breast surgery for Stage IV breast cancer (910), breast surgery in advanced breast cancer has often been limited to resections that aim to control ulcerating and fungating tumors that are resistant to non-operative interventions (911). The inclusion of patients generally presenting with a more advanced disease state may contribute to the protective effect of surgery on the risk of cardiovascular disease observed in this study. If the risk estimate of HF associated with breast surgery was adjusted for the presence of a secondary tumor, the risk of cardiovascular disease slightly increases, but surgery remains associated with an unexplained protective effect (aOR= 0.515, 95% CI: 0.435, 0.610). Although further investigation might ultimately explain this anomaly, the risk of cardiovascular disease associated with ETs remains statistically significant regardless of adjustment for breast surgery.

PPIs have been used for the prevention of chemotherapy-induced gastro-esophageal reflux and gastroduodenal injuries (912), and were shown to sensitize cancer cells to chemotherapies (913) (914) (915). Cardiovascular risks associated with PPI treatment have been documented (916), even though there remains controversy about the

actual level of risk (917). Our study has shown a high proportion of PPI use and an association between use of PPIs and the cardiovascular outcomes of interest. Studies have shown that this class of drug can reduce the elimination of chemotherapeutic agents in the plasma of cancer patients (918). PPIs could potentially lead to adverse cardiovascular outcomes both through intrinsic cardiotoxicity and maintenance of cytotoxic drugs within the systemic circulation. Further studies are required to better characterise the cardiovascular disease risks associated with PPIs in breast cancer patients. Moreover, a significant association has been reported between estrogen treatment, the diagnosis of gastro-esophageal reflux and PPI use (919), suggesting a possible correlation between use of PPIs and estrogen levels. The reported association between PPI and cardiovascular disease and PPI use with estrogen treatment underpins inclusion of proton pump inhibitors as a covariate in the final multivariate logistic regression analysis for the both risk of MI and HF associated with ETs.

Our study has several strengths. First, the heterogeneous population of BC patients examined presented with additional co-morbidities beyond those typically seen in randomized clinical trials. Second, the potential confounding effect of 22 therapeutic, comorbid and socio-demographic factors were taken into account. Accordingly, the observed increase in cardiovascular risk following AI exposure could not be explained by imbalance in exposure to risks factors such as anthracyclines, trastuzumab or comorbidities. Third, this study is not based on direct comparison of AIs with SERM/DRs as

controls are selected from the overall BC population, limiting the likelihood that the reported protective effect of tamoxifen be responsible for the apparent increase in cardiovascular events with AIs. Fourth, the requirement of six months of recorded care prior to the index date allows for the identification of cardiovascular risk factors before the diagnosis of BC, which were taken into account in the multivariate analysis.

Our analysis also has a number of limitations. First, since the study relies on ICD-9-CM diagnosis codes, any underreporting or miscoding could influence the accuracy of the results. Second, because the analysis relies on data availability, any missing data could have a marked impact on the results. Third, since the Cerner HealthFact™ Datawarehouse reflects predominantly hospital encounters, this analysis considers prescriptions filled primarily within the hospital setting; as a consequence, not all encounters with medications otherwise dispensed may have been captured. Accordingly, encounters with SERMs and AIs may be underrepresented, as these drugs are usually administered daily over a period of several years. Fourth, Caucasian patients from the Northeastern region are over-represented in this study, limiting the generalizability of the results to the overall US population. Lastly, there remains a possibility of residual confounding as a consequence of not having data on other potential risk factors for cardiovascular diseases such as body mass index, smoking and level of physical activity.

This analysis corroborates the findings of another recent observational study (634) which indicated that AIs may be associated with cardiovascular disease risk independently of other risk factors in a heterogeneous population of BC patients. Additional studies are needed to further characterise this risk profile.

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Authors' disclosures of potential conflicts of interest

D. Krewski and D. Mattison serve as Chief Risk Scientist and Chief Medical Officer for Risk Science International (RSI), a Canadian company established in 2006 in partnership with the University of Ottawa (www.risksciences.com). Although unrelated to the present paper, RSI has conducted work on pharmaceutical products for public sector clients. D. McNair is the President of Cerner Math Inc. and has ownership interest in Cerner Corporation.

Chapter 5

Off-label use of cancer therapies in women diagnosed with breast cancer in the United States

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Description and statement of contributions of collaborators and co-authors

This manuscript uncovers the extent of off-label use in a population of female breast cancer patients and establishes whether this therapeutic use was evidence-based. The association of various socio-demographic, treatment centre, and disease characteristics with off-label use is also investigated.

S. Hamel performed all SAS coding and literature search required for this manuscript with guidance from Dr. Krewski. The level of evidence for off-label use (**Table *25***) was independently reviewed by S. Hamel and Dr. D. Mattison as well as Dr. Nathalia Shilnikova. All tables were created by S. Hamel. The text was written by S. Hamel with review and editing from Dr. D. Krewski, Dr. A. Krantis, Dr. D. McNair, Dr. D. Mattison, and Dr. N. Birkett.

Abstract

Purpose

To determine the level of off-label cancer therapy use in a population of female breast cancer patients and to establish whether this use was evidence-based.

Methods

A study was conducted by sampling Cerner's datawarehouse for all women diagnosed with breast cancer between January 2000 and June 2009 who received at least one cancer therapy approved by the US-FDA during the study period. Drug encounters were considered off-label if the circumstances of use did not match the age or medical diagnoses specified on the product label at the time of study. The level of evidence for the use of these drugs in a breast cancer setting was evaluated from randomized phase III trials using a three tiered approach.

Results

The study included 2,663 women with a median age of 59 years. A total of 1,636 off-label encounters were recorded, representing 13.0% of all encounters. Of the 65 cancer

therapies investigated, 55.4% were prescribed off-label. The drugs with the highest off-label use were, in a descending order, vinorelbine, carboplatin, bevacizumab, leuprolide, liposomal doxorubicin and cisplatin. Most off-label encounters were evidence-based and more likely to be associated with private insurance coverage, younger age, ethnicities other than Caucasian, smaller treatment centres and drugs with limited labeled indications that have a longer market history.

Conclusions

Off-label prescribing is common practice in oncology and is an integral component of breast cancer treatment strategies. While this practice tends to be associated with specific socio-demographic factors and disease characteristics, the majority of off-label encounters appear to be evidence-based decisions.

Introduction

All prescription drugs are labeled in accordance with the circumstances of use and evidence collected from randomized controlled clinical trials. However, once a drug reaches the market, a physician may exert clinical judgement and prescribe drugs for other conditions or circumstances. This type of prescribing is considered 'off-label' and has become part of mainstream medical practice extending beyond the specifications of the drug label (920) (921) (922).

Off-label use in breast cancer has been previously reported (922) (923), but only one study has focused on the off-label chemotherapeutic use in women over 65 years old diagnosed with breast cancer between 1991 and 2002 (924). Although off-label use of chemotherapy has been reported, breast cancer patients are treated with a wide variety of agents which are not considered typical chemotherapies. The discovery of distinct molecular determinants of tumor development and progression has opened a new era of targeted therapies. Investigating the extent of off-label use, taking into consideration the broader range of therapies available and extending the analysis to the overall breast cancer population, regardless of age, may provide insight into the scope of this practice.

Consequently, we sought to estimate the extent of off-label use of any chemotherapies, targeted agents, hormone therapies, and immunotherapies approved by the FDA as a cancer therapy at the time of this study and investigate whether drug coverage or factors such as patient demographics, drug, treatment centre and physician characteristics influence off-label prescribing among breast cancer patients.

Methods

Data source

All female patients from the Cerner HealthFacts™ Datawarehouse diagnosed with breast cancer (ICD-9-CM 174, 238.3, 239.3) from January 2000 to June 2009 who received at least one cancer therapy in a hospital setting during this period were considered for inclusion in this study. At the time of the analysis, HealthFacts™ contained information on distinct inpatient admissions, emergency department, and outpatient visits from 114 hospitals and clinics throughout the United States.

Study eligibility criteria

For each patient, the date of the earliest breast cancer diagnosis was designated as the index date. Those who had less than 6 months recorded care prior to the index date were excluded because they were considered less likely to have their breast cancer therapies and potential comorbidities completely recorded. The study was limited to those at least 20 years of age as of their index date.

Identification of anticancer therapy under study

Any medication approved by the FDA during the follow-up the period for its anticancer properties was considered for inclusion and was classified as chemotherapy, targeted therapy, hormone therapy, or immunotherapy based on its mechanism of action as per **Table *19***. The chronological FDA-approval history for each drug in a given therapeutic class was validated through the FDA's Drug Approvals and Databases. To be considered, the drug and its labeled indications had to be endorsed by the FDA at the time of the study. Drugs and indications that were approved during the study period were also included.

Table 19: Categories and subcategories of cancer drugs considered for analysis. All therapies in these categories and subcategories that were FDA-approved for a cancer indication during the study period were evaluated

Category	Subcategory
Chemotherapies	Alkylating agents, Antimetabolites, Anti-tumor antibiotics, Topoisomerase inhibitors, Anti-mitotic agents
Hormone therapies	Estrogen receptor modulators, Aromatase inhibitors, Anti-androgens, Gonadotropin-releasing hormone agonists or analogs, Progestins, Somatostatin analogs
Targeted therapies	Small-molecule inhibitors, Differentiating agents
Immunotherapies	Monoclonal antibodies, Non-specific immmunotherapies and adjuvants, Immunomodulators

Determination of off-label status

For the purpose of this study, we ascribed off-label status to all drug uses which met at least one of the following criteria: (1) none of the ICD-9-CM codes in the patient's electronic record during the study period could be matched to any labeled indications of the prescribed drug (**Table *20*** and **Table *21***), or (2) the age of the recipient differs from the label specifications (**Table *22***). An attained age of 50 years was used as an indicator of post-menopausal status as described elsewhere (876) (877) (878). Off-label uses related to sequential or concomitant therapies, dosage, duration of treatment, or route of administration were not considered. The main source for determining labeled indications were the drug labels at the time of use found on the FDA website.

For each drug encounter, all associated ICD-9-CM codes, regardless of their diagnostic priority, were considered to determine the indication for use. If none of the ICD-9-CM codes specific to the drug encounter were labeled indications, the overall ICD-9-CM diagnosis information for the patient was investigated. If the patient had never been diagnosed with a condition approved by the FDA for the specific drug, the use was considered off-label. Encounters with drugs that have obtained FDA approvals for new indications during the study period were considered off-label before the official approval date. For labeled indications that could not be accurately coded using the ICD-9-CM system,

all codes related to the condition were adopted. For example, since no official ICD-9-CM diagnosis codes exist to specify cancer subtypes expressing a particular tumor marker, the ICD-9-CM codes for breast cancer (ICD-9-CM 174, 238.3, 239.3) were considered labeled indications for therapies indicated for breast cancer tumors overexpressing Her-2. Drugs considered and approved by the FDA at the time of study but not prescribed to the studied patient population are listed in **Table *23***.

Table 20: Summary of FDA-approved chemotherapeutic agents investigated in current study by category and subcategory

Drug category	Drug name	Indicated for Breast cancer	Labeled indications if not indicated for breast cancer (ICD-9 codes)	Initial FDA approval during study period
Alkylating agents	Carboplatin		183, 198.6	1989
	Carmustine		191, 200-202, 203.0	1977
	Chlorambucil		200-202, 204.1, 204.9	1957
	Cisplatin		183, 186, 188, 198.6	1978
	Cyclophosphamide	Yes		1959
	Dacarbazine		172, 198.2, 201	1975
	Ifosfamide		186	1988
	Mechlorethamine		162.2-162.5, 162.8, 162.9, 197.0, 200, 201, 202.0, 202.1, 202.8, 204.1, 205.1, 208.1, 238.4, 511.9	1949
	Melphalan		183,[1] 198.6,[1] 203.0	1964
	Oxaliplatin		153, 154, 197.5	August 2002
	Streptozocin		157.4	1982
	Thiotepa	Yes		1959
Antimetabolites	Azacitidine		205, 280-285	May 2004
	Capecitabine	Yes		1998
	Cladribine		202.4	1993
	Clofarabine		204.0, 204.9	December 2004
	Cytarabine		204.0, 204.9, 205.0, 205.1, 205.9	1969
	Fludarabine		204.1, 204.9	1991
	Fluorouracil	Yes		1962
	Gemcitabine	Yes[2]	157.0-157.9, 162.2-162.5, 162.8, 162.9, 197.0[3]	1996
	Hydroxyurea		172.1-172.4, 173.1-173.4, 183, 195.0, 198.2, 198.6, 205.1, 205.9	1967
	Mercaptopurine		204.0, 204.9	1953
	Methotrexate	Yes		1953
	Pemetrexed		162.2-162.5, 162.8, 162.9, 163, 197.0	February 2004
Anti-tumor antibiotics	Bleomycin		140-149, 160, 161, 180, 184, 186, 187, 195.0, 197.2, 198.82, 200-202, 511	1973
	Dactinomycin	Yes[4]		1964
	Daunorubicin		204.00-204.91, 205.00-205.21, 205.80-205.91, 208.00-208.01	1979
	Doxorubicin	Yes		1974
	Epirubicin	Yes		1999
	Idarubicin		205.0, 205.9	1990
	Liposomal doxorubicin		176, 183, 198.6, 203.0	1995
	Mitomycin-C		151, 157	1981
Topoisomerase inhibitors	Etoposide		162.2-162.5, 162.8, 162.9,186, 197.0	1983
	Irinotecan		153, 154, 197.5	1996
	Mitoxantrone		185, 205-208, 340	1987
	Topotecan		162.2-162.5, 162.8, 162.9, 180, 183, 197.0, 198.6	1996
Anti-mitotic	Docetaxel	Yes		1996
	Ixabepilone	Yes		October 2007
	nab-Paclitaxel	Yes		January 2005
	Paclitaxel	Yes		1992
	Vinblastine	Yes		1965
	Vincristine		171, 189.0, 189.9, 194.0, 194.9, 198.0, 200, 201, 202.0, 202.1, 202.8, 204.0, 204.9	1963
	Vinorelbine		162.3-162.5, 162.8, 162.9	1994

[1] Indiction for the oral formulation

[2] FDA-approved for breast cancer on December 18, 2004

[3] Indications approved by th FDA before December 18, 2004. Ovarian cancer only included after it was approved by the FDA on July 14 2006

[4] Not breast cancer specifically but locoregional solid tumors

Table 21: Summary of other FDA-approved anticancer therapies investigated in current study by category and subcategory

Drug category	Drug name	Indicated for breast cancer	Labeled indications if not indicated for breast cancer (ICD-9-CM codes)	Initial FDA approval during study period
Hormone therapies	Anastrozole	Yes		1995
	Exemestane	Yes		1999
	Fluoxymesterone	Yes		1956
	Fulvestrant	Yes		April 2002
	Goserelin	Yes		1989
	Letrozole	Yes		1997
	Leuprolide	No	185	1985
	Tamoxifen	Yes		1977
Targeted therapies	Bortezomib	No	200.4, 203.0	May 2003
	Erlotinib	No	162.2-162.5, 162.8, 162.9, 197.0	November 2004
	Imatinib	No	150-154, 158.0, 159.0, 159.8, 159.9, 171.5-171.9, 205.1, 205.9, 238.1, 239	May 2001
	Sorafenib	No	155.0, 155.2, 197.7, 189.0, 189.1, 189.8, 189.9, 198.0	December 2005
Immunotherapies	Aldesleukin	No	172, 189.0, 189.1, 189.8, 189.9, 198.0, 198.2	1992
	Alemtuzumab	No	204.1, 204.9	May 2001
	Bevacizumab	Yes[1]	153, 154, 162.2-162.5, 162.8, 162.9, 191, 197.0, 197.5, 198.3	February 2004[2]
	Cetuximab	No	140-149, 153, 154, 160, 161, 173.0-173.4, 195.0, 197.5	February 2004
	Denileukin diftitox	No	202.1, 202.2	1999
	Gemtuzumab ozogamicin	No	205.0, 205.9	2000
	Panitumumab	No	153, 154, 197.5	September 2006
	Rituximab[3]	No	200, 202, 204.1, 204.9, 714	1997
	Thalidomide	No	0.17.1, 695.2, 203.0	1998
	Trastuzumab	Yes		1998

[1]Breast cancer indication approved by FDA on February 22, 2008 and revoked in November 2011

[2]Colorectal cancer indication approved in February 2004, Non-small cell lung carcinoma in October 2006, Glioblastoma in May 2009

[3]Obtained FDA approval for Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA) only in April 2011 (post-study period)

Table 22: Age as per FDA-approved product label for drugs under study with such specification

Drug name	Labeled age (years)[1]
Clofarabine	1-21
Fluoxymesterone	≤50
Goserelin	≤50
Anastrozole	≥50
Exemestane	≥50
Fulvestrant	≥50
Letrozole	≥50
Gemtuzumab ozogamicin	≥60

[1]For the purpose of this study, age of menopause was fixed at 50 years

Table 23: Other FDA-approved anti-cancer therapies at the time of study but not used in the studied population

Category	Drug name
Chemotherapies	Altretamine, Asparaginase, Bendamustine, Busulfan, Decitabine, Estramustine, Floxuridine, Liposomal Cytarabine, Lomustine, Nelarabine, Pegaspargase, Pentostatin, Procarbazine, Temozolomide, Teniposide, Thioguanine, Valrubicin
Hormone therapies	Bicalutamide, Degarelix, Flutamide, Histrelin, Nilutamide, Toremifene, Triptorelin
Targeted therapies	Dasatinib, Everolimus, Lapatinib, Nilotinib, Sorafenib, Temsirolimus, Vorinostat, Bexarotene, Tretinoin
Immunotherapies	BCG, Ibritumomab, Imiquimod, Interferon alfa-2a, Lenalidomide, Tositumomab

Level of evidence

The six drugs with the highest off-label use were subjected to a more detailed investigation. The off-label uses were categorised as breast cancer specific if (1) a breast cancer diagnosis was associated with the drug encounter, and (2) no other malignancies or known labeled conditions were diagnosed as part of the same encounter (excluding

secondary malignant neoplasms defined by ICD-9-CM 196-198). An extensive search of Medline, U.S. FDA clinical reviews, and drug/disease-state databases (UptoDate online, MICROMEDEX) was conducted to further characterize the level of evidence for the off-label uses. All six drugs investigated had evidence derived from at least one well-designed randomized, phase III clinical trial (RCT) in a breast cancer population. All applicable published evidence derived from these RCTs, including those with negative or equivocal findings, were used to rate the overall evidence available for each off-label drug-indication pair. Categorization of available evidence was conducted independently by two of the authors (SH and DM) as well as an independent reviewer using the following three tiered approach: 1) 'sufficient' evidence was derived when at least five RCTs reported reasonable evidence of therapeutic benefit in breast cancer setting; 2) 'limited' evidence was extracted from at least one RCT but the conclusions from overall findings are inconsistent; and 3) 'inadequate' evidence was derived when no RCT reported benefit or non-inferiority when compared to the standard chemotherapy regimen.

Statistical analysis

The level of off-label use was calculated by dividing the number of off-label drug encounters by the total number of encounters for a given drug and therapeutic class. Additionally, the number of drugs used under off-label circumstances was calculated using all drugs within a given therapeutic category or subcategory as a denominator. Variation in

the percentage of off-label encounters with patient age, ethnicity, marital status, source of payment, census region, bed size range, physician's specialty, the date of market approval for a drug, and the number of approved indications was examined using chi-square tests. All analyses were conducted using SAS software (Version 9.2, SAS Institute, Cary, NC).

Results

Number of drugs used beyond the label specifications

Among the 107 drugs considered in this study, 43 chemotherapies and 22 other cancer therapies were administered to a population of 2,633 breast cancer patients totaling 14,586 drug encounters. Only 21 (32.3%) of these therapies were indicated for breast cancer during the full study period or at the time of their first introduction to the market. Gemcitabine was approved by the FDA for breast cancer in December 2004. Accordingly, all gemcitabine encounters which occurred before that date were considered off-label if no indication listed in **Table *20*** was diagnosed. It is of note that, although the FDA revoked breast cancer as an indication for bevacizumab on November 18, 2011 (95), breast cancer was considered a labeled indication from the original approval date for this indication (February 22, 2008) until the end of the study period. A total of 36 drugs (55.4% of all cancer therapies administered) were used either for an off-label indication or by a recipient whose age differs from the label specifications. A total of 13.0% of patients received at least one cancer therapy under these off-label circumstances.

Off-label use by drug category

The frequency of off-label use of chemotherapy and other drugs was similar (55.8% and 54.5%). However, off-label patient encounters was almost double for chemotherapy

compared to other drugs (14.1% vs 8.4%) (**Table *24***). Topoisomerase inhibitors and alkylating agents were the classes of chemotherapies with the highest proportion of off-label use, whereas the targeted agents ranked first for the other cancer therapies.

Table 24: Number of off-label drugs and encounters for each drug category and subcategory

Category	Number off-label drugs (%)[1]	Off-label encounters (%)[2]	Subcategories	Number Off-label drugs (%)[2]	Off-label encounters (%)[2]
Chemotherapies	24 (55.8%)	1153 (14.1%)	Topoisomerase inhibitor	4 (100%)	61 (27.9%)
			Alkylating agents	7 (58.3%)	485 (26.2%)
			Anti-metabolites	8 (61.5%)	103 (8.5%)
			Anti-tumor antibiotics	3 (37.5%)	75 (6.3%)
			Anti mitotics	2 (28.6%)	429 (11.6%)
Other agents	12 (54.5%)	483 (8.4%)	Targeted therapies	2 (50.0%)	11 (37.9%)
			Immunotherapies	5 (45.5%)	233 (8.2%)
			Hormone therapies	5 (62.5%)	239 (8.2%)

[1]Expressed as a percentage of all drugs including those indicated for breast cancer in a given therapeutic category or subcategory

[2]Expressed as a percentage of all encounters including those indicated for breast cancer in a given therapeutic category or subcategory

Age-related off-label use

Only 8 drugs which we considered had age-related restrictions applied by the FDA when they granted approval (either limiting approval based on age or to a particular age-related event such as menopause). Most encounters with these drugs (96.4%) were in line with the age-related label specifications. Although clorafarabine is indicated for use in pediatric patients with acute or relapse lymphoblastic leukemia, all reported encounters involved patients over the age of 21 diagnosed with other off-label indications than breast cancer.

Level of evidence

If we only consider therapies not specifically indicated for the treatment of breast cancer, 55.5% of drug encounters recorded in the database can be categorised as off-label on the basis of indication for use. The drugs with the highest number of off-label uses were, in descending order, vinorelbine, carboplatin, bevacizumab, leuprolide, liposomal doxorubicin, and cisplatin (**Table *25***). Overall, 93.3% of these off-label drug encounters were associated with a diagnosis of breast cancer. The pattern of off label-use appeared to be aligned with the available evidence to support the use. The level of evidence derived from the drug with the highest off-label use, vinorelbine, was considered to be sufficient to support its use in a breast cancer setting. During the study period, the other five drugs with the highest off-label use were considered to have limited evidence to support their use in a breast cancer population, including bevacizumab which obtained market approval for this indication in February 2008 and was subsequently revoked by the FDA in November 2011 after concluding that the drug has not been shown to be effective or safe for that use.

Table 25: Level of evidence for the 6 drugs with the highest off-label use

Drugs	Total	Total Off-label (%)	BC specific off-label	Level of evidence	Primary ICD9 diagnosis code other than BC
Vinorelbine	732	413 (27.0%)	395	Sufficient	147, 184.4, 188, 202.8, 204.1
Carboplatin	444	382 (25.0%)	338	Limited	147, 162, 182, 191, 202.88, 235.7
Bevacizumab[1]	324	199 (13.0%)	222	Limited	162.9, 184.4, 191.9[2], 202.8
Leuprolide	136	133 (8.7%)	122	Limited	171, 173.3
Liposomal Doxorubicin	104	67 (4.4%)	59	Limited	162.8, 171.9, 202.8
Cisplatin	68	48 (3.1%)	23	Limited	149.8, 150, 151, 162, 170.3, 173.3, 182, 195.0, 201, 202.8, 203,

The total number of off-label encounters and percentage of total encounters is listed for each drug. The level of evidence and recommendation for the off-label use associated to a breast cancer diagnosis were graded as Sufficient, Limited or Inadequate based on the source and strength of the evidence available during the study period. If the off-label encounter was associated to another condition, the ICD-9-CM code was recorded.

[1]All bevacizumab encounters before February 22, 2008

[2]Glioblastoma indication approved by FDA (May 05, 2009) after the drug was administered

BC = breast cancer

Patient demographics

The median age of the study population was 59 years. Drug encounters were more likely to be off-label among younger women (<50 years age) (16.2%), whereas encounters for patients in the older age group (≥75 years) were less common (7.4%). There were more off-label encounters among African American breast cancer patients and patients with other ethnic backgrounds than among Caucasian patients. There was no apparent relationship between marital status and the off-label administration of cancer therapies.

Drug characteristics and insurance coverage

Off-label use was inversely related to the number of labeled indications specific to the drugs under study. Drugs with only one or two labeled indications were more likely to be involved in an off-label drug encounter. The date of market approval was also predictive of off-label use, with therapies approved by the FDA between 1981 and 1990 being more likely to be with linked to off-label use. The information about drug coverage plans was missing for a large proportion of encounters (77.4%); however, considering only encounters for which insurance information is available, Blue Cross was more strongly associated with off-label use.

Treatment centre and physician characteristics

Although 114 treatment centres were contributing to the database at the time of the study, 67 distinct healthcare institutions provided electronic records of drug encounters meeting the criteria of the study. Of these institutions, most administered cancer therapies in accordance with the label specifications (66 centres), while 47 centres dispensed at least one therapy under off-label circumstances. This practice was more common in treatment centres located in the Northeastern region of the United States, whereas institutions in the Midwest were less likely report this type of use. Smaller centres with a limited number of beds were more likely to administer drugs in an off-label fashion; this practice was less likely in medium size institutions (199-399 beds). Specialists were more inclined to

prescribe chemotherapies and other cancer therapies, but none of the physician types appeared to be associated with increased off-label use.

Table 26: Demographic, treatment centre, insurance coverage and drug characteristics comparison between on-label and off-label encounters. Expressed as the number and percentage of off-label encounters.

Variable	Variable category	Off-label (%)
Age*	15-49	621 (16.2%)
	50-64	396 (10.4%)
	65-74	432 (9.7%)
	75+	187 (7.4%)
Ethnicity*	Caucasian	1113 (10.3%)
	African American	185 (13.0%)
	Other	95 (15.3%)
	Unknown	243 (14.4%)
Marital status	Married	338 (11.0%)
	Other	1293 (11.3%)
	Unknown	5 (10.4%)
Prescription drug converage*	Medicare	209 (9.5%)
	Medicaid	81 (10.4%)
	HMO/PPO	24 (6.9%)
	Blue Cross	65 (15.3%)
	Self-pay	21 (11.0%)
	Other	75 (12.3%)
	Unknown	1161 (11.6%)
Census region*	Midwest	255 (8.9%)
	South	264 (11.4%)
	Northeast	1088 (12.0%)
	West	29 (9.0%)
Bed size*	1-99	477 (16.2%)
	100-199	48 (5.7%)
	200-299	315 (10.0%)
	300-499	234 (9.4%)
	500+	562 (10.9%)
Physician type*	Specialists	751 (10.9%)
	Surgeons	22 (5.9%)
	Generalists	28 (6.3%)
	Unknown	835 (12.1%)
Number of approved indications*	1-2	1395 (27.6%)
	3-4	206 (3.1%)
	5-7	34 (9.5%)
	8+	1 (0.0%)
Date of FDA approval*	Before 1981	130 (3.2%)
	1981-1990	602 (78.7%)
	1991-2000	635 (7.8%)
	2001-2009	269 (16.1%)

*Differences amongst categories for this variable are significantly different ($p<0.00001$) based on a chi-square test of homogeneity

Discussion

In the present study, 13.0% of women with breast cancer were prescribed at least one cancer therapy under off-label circumstances, less than the 35% reported previously (924). This difference may be related to the greater diversity of patients and types of therapies considered in our investigation, as well as the disparity between the two study periods. Several drugs were approved by the FDA between 2002 and 2009, including 4 drugs with a labeled breast cancer indication (bevacizumab, gemcitabine, ixabepilone and nab-paclitaxel). The introduction of new medications on the market and the approval of new indications for established drugs may also explain the smaller proportion of women who experienced off-label use in our study, especially since gemcitabine was listed as the second drug with the most off-label use in the previous investigation. In agreement with previous research, vinorelbine demonstrated the highest proportion of off-label use. Off-label and subsequently labeled encounters with bevacizumab was sustained throughout this study. It would be interesting to determine if the use of this drug for treatment of breast cancer has decreased since the FDA revoked this indication from the product label on November 18, 2011.

A previous report showed appreciable geographic variation in prescribing patterns in the US (925). In the present paper, about two thirds of encounters were recorded in

treatment centres located in the Northeastern census region, which includes 46 of the 114 treatment centres in the HealthFact™ database. Since this region represented 19% of the US population in the 2000 census (901), the data may not be fully representative of overall off-label prescribing practice in the US.

Although specialists were more likely to prescribe cancer therapies, no notable differences were observed in off-label prescribing habits by physician type, an observation which differs from a previous report which focused on a pediatric population, a vulnerable subgroup rarely included in clinical trials (926). Accordingly, the scarcity of evidence to support pediatric off-label use for certain indications may partially explain why specialists, who are most familiar with the patient's condition, were more inclined to prescribe off-label. Off-label therapy may also be a last resort for patients exhibiting poor prognoses and limited therapeutic options, regardless of physician type.

Off-label encounters were more common in younger compared to older patients. There was no apparent relationship between off-label encounters and marital status, although off-label encounters were more prevalent among non-Caucasians. While other studies have shown racial difference in breast cancer treatment decisions (927) (928), the literature is ambivalent regarding the association between race and off-label prescribing (926) (928) (929).

As in previous research, we observed that medications with the fewest labeled indications had the highest rate of off-label use (930). Therapies approved in the 1980's were more likely to be used off-label, possibly because older drugs will have had greater opportunity for discovery of new evidence to support off-label use (931) (932). Since these drugs no longer enjoy patent protection, it is unlikely that a randomized clinical trial to provide evidence to support a new indication will be undertaken. Of the 12 new drugs approved by the FDA for the treatment of cancer between 1981 and 1990, only one was indicated for breast cancer; this may explain the high off-label use observed (78.7%) for drugs originally approved during this decade. Drugs marketed before 1981 were less likely to be prescribed off-label, even though physicians may be more familiar with these drugs; these drugs tended to have a higher number of labeled indications, thereby decreasing the likelihood of being prescribed off-label. Private insurers such as Blue Cross demonstrated greater off-label use than public insurers, as reported previously (929), possibly due to government policies restricting access to therapies.

Study strengths include (1) the availability of data from different insurers (2) inclusion of all, not just post-menopausal, breast cancer patients (3) consideration of age in determining off-label use, and (4) the investigation of all approved cancer therapies, not just chemotherapies.

Our study also has a number of limitations. (1) Because ICD-9-CM codes were used in identifying off-label use, any underreporting or miscoding could affect the accuracy of the results. (2) Missing data could influence the results. For example, information on insurance coverage was unavailable for more than 70% of drug encounters. For the purpose of this study, it was assumed that the distribution of the missing information was proportional to that observed within the available data. (3) Since treatment centres in the Northeast region were overrepresented, results may not be representative of overall off-label practice in the United States. (4) Since the data were collected from hospital encounters, this analysis only considers prescriptions filled within the hospital setting; encounters with medications dispensed outside of this setting were not captured. Accordingly, encounters with oral medications such as endocrine therapies may be underrepresented as these drugs are often administered daily over a period of several years. (5) The chi-square tests used evaluate the significance of differences in off-label use with respect to the demographic, treatment centre, insurance coverage, and drug characteristics in Table 6 do not take into account the correlation among repeated encounters with the same patient. However, it is unlikely that even a high degree of correlation among repeat encounters would render these significant differences non-significant ($P>0.05$). (6) The association between different disease characteristics and off-label use was not assessed since information on tumor stage, grade, and tumor markers was unavailable. (7) The definition of off-label was conservative, since concomitant or sequential medication, dosage, frequency, route of administration, and duration of treatment were not considered in this analysis.

Conclusion

Our study corroborates and expands on previous findings to suggest that off-label use of cancer therapies is widespread among patients with breast cancer and that the majority of these encounters have some evidence to support their use. Socio-demographic, insurance coverage, treatment center, and physician and drug characteristics appeared to influence off-label prescribing patterns. More research is warranted to determine whether the practice of off-label prescribing in the context of cancer treatment yields substantial clinical benefits. In the interim, decisions to prescribe a therapy under off-label circumstances should be evidence-based in an effort to achieve therapeutic benefit and to minimize the risk of possible adverse reactions associated with these therapies.

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Authors' disclosures of potential conflicts of interest

D. Krewski and D. Mattison serve as Chief Risk Scientist and Chief Medical Officer for Risk Science International (RSI), a Canadian company established in 2006 in partnership

with the University of Ottawa (www.risksciences.com). Although unrelated to the present paper, RSI has conducted work on pharmaceutical products for public and private sector clients. D. McNair is the President of Cerner Math Inc. and has ownership interest in Cerner Corporation.

Chapter 6

6. Discussion

The body of work presented in this thesis corroborates and expands on previous findings that aromatase inhibitors are associated with cardiovascular risks, and that off-label administration of oncology products is widespread in the treatment of breast cancer. These observations should be considered when weighing the relative risks and benefits for informed decision making regarding the most appropriate treatment option for breast cancer patients.

6.1 Understanding the mechanisms of drug-induced cardiotoxicity to better predict clinical outcome

Cardiotoxicity is multifactorial pathophysiological process which has been implicated in 31% of drug withdrawals from the US market (933). One of the more prominent examples is the voluntary withdrawal of rofecoxib due to an increase in risk of MI and stroke (934). The large number of drugs with undetected adverse cardiovascular

risks in preclinical studies underscores the need for additional predictive safety screens in the early phases of the drug discovery process. As discussed in Chapter 2, drug-induced cardiovascular damage ultimately results in a series of molecular and physiological changes leading to the manifestation of a serious clinical outcome such as MI or HF. Increased understanding of these mechanisms may be useful indicators of the clinical safety profile of antineoplastic drugs. This mechanistic approach was adopted by the US National Research Council in their new toxicity testing framework which emphasizes the use of high throughput *in vitro* assays and computational models to assess the risk associated with pharmaceutical compounds and environmental contaminants (935).

In chapter 3, we reported that SERMs have antioxidant properties with respect to lipid peroxidation *in vitro,* and that tamoxifen has a beneficial effect on circulating lipids both *in vivo* and in clinical settings. Such cardioprotective mechanisms have not been described following exposure to AIs. Moreover, absence of estrogen production was shown to be associated with cardiac hypertrophy and impaired cardiac function which sensitizes the heart to pathological insults through the up-regulation of hypertrophic pathways (660) as well as modulation of the renin-angiotensin-aldosterone system, leading to high aldosterone concentrations and high blood pressure (667) (668) (669). In accordance with these mechanistic observations, we found that only AIs were associated with an increased risk in heart failure in a nested case-control study (Chapter 4).

Predictive models of drug-induced cardiotoxicity and pharmacovigilance systems have been developed and offer certain advantages in comparison to the classical clinical trial approach (936) (937). Based on the assumption that drug-induced prolongation of the QT interval is frequently associated with modulation of repolarization via potassium channels, experimental and computational models of the potassium channel hERG (human ether-a-go-go-related gene) have been used in the preclinical assessment of drug-induced ventricular arrhythmia (937).

Despite the plethora of empirical models available, many uncertainties about the accuracy of simple cellular systems limit their clinical applicability (938). Our limited ability to translate observations across model systems is a major obstacle to the success of preclinical models (939). Attempts to reduce oxidative stress in patients treated with doxorubicin were not associated with the anticipated reduction in cardiovascular disease risk, even though oxidative stress has been established as the main mechanism of doxorubicin-induced cardiotoxicity (940). Despite some limitations, *in vitro* models of cardiotoxicity have been used to predict the cardiovascular effects of several marketed kinase inhibitors (941) and computational analyses found mechanistic convergence in drug-induced cardiotoxicity regardless of the cardiotoxic phenotype (939).

Further validation would greatly enhance the applicability of molecular mechanisms as a predictive tool for drug-induced adverse events and our ability to mitigate cardiotoxicities associated with oncology drugs. Nonetheless, since not all adverse outcomes are detected before drugs are approved for the market, understanding the mechanisms of drug-induced cardiotoxicity can complement reports of suspected adverse drug reactions and support the need for active surveillance of certain drugs.

6.2 Exposure to AIs is associated to an increase in risk of HF

The results of the nested case-control study in Chapter 4 have shown that although ETs are not associated with increase in risk of MI, AIs may pose a greater risk of HF than SERM/DRs; this increased risk remained statistically significant, even after consideration of the potential confounding effects of 22 covariates reflecting socio-demographic, comorbidities, disease, and treatment characteristics. Although some of these comorbidities could be on the causal pathway and adjustment could mask the cardiovascular effect of ETs, none of these comorbidities changed the risk estimate by more than 10% (expect for the risk of MI associated with SERM/DRs which was altered by slightly more than 10% after adjustment for hypertension). Accordingly, hypertension, hyperlipidemia and diabetes were not retained in the final adjusted model.

Although it would have been informative to consider duration and intensity of exposure, in addition to the fact of exposure (ever/never exposed), our ability to operationalize exposure as a continuous variable was limited to the data available for analysis. Only treatment encounters recorded in hospital settings were accessible, rendering assessment of treatment duration and treatment interruptions difficult. The uncertainty surrounding exposure accuracy may have led to an unmeasurable time bias. Although this analysis does not address the issue of adherence and persistence with treatment, cancer patients on long-term therapy are generally highly motivated to remain adherent because of the seriousness of the underlying disease and the potential risk associated with non-adherence. A review of studies looking at adherence to oral anti-neoplastic agents showed adherence rates ranging from 20% to 100% (942). The adherence rates for ETs in clinical trials for early breast cancer are considered to be relatively high (in the range of 72-78%) when compared to the average reported adherence rates for drugs in general (943). Since adherence rates of less than 80% have been shown to have significant impact on prognosis (944), physicians should sensitize patients to the importance of treatment adherence. For the study presented in Chapter 4, an intent-to-treat analysis based on the fact of exposure was used. Accordingly, exposure status was assumed to be constant throughout the follow-up period beginning at the time of first exposure.

Although exposure to SERM/DRs and AIs were investigated independently in this study, these classes of ETs can be used sequentially. In a sensitivity analysis, we found that 2 patients in the MI case-control study and 21 patients in the HF case-control study were exposed to both ETs classes during the study period. Exclusion of these patients from the analysis did not significantly affect the risk estimates for the cardiovascular outcomes of interest.

This study provides additional insight on the safety profile of aromatase inhibitors in a context that is not directly comparing the effects of AIs to those of tamoxifen. Most clinical studies investigating the cardiovascular risks associated with ETs are comparative trials of patients treated with AIs vs tamoxifen. Since cardioprotective properties are associated with tamoxifen use, comparative studies have attributed the increase in cardiovascular risks observed with AIs as an indirect observation of the protective properties of tamoxifen. Our study has examined the risk of AIs and SERM/DRs independently and still found a significant increase in risk of HF following AIs exposure. This analysis corroborates the findings of another recent observational study (634), and suggests that the risk should be further characterised in well-designed large scale outcome studies.

6.3 Potential role of PPI in the development of cardiovascular disease

An interesting finding of our observational studies is the increase in cardiovascular risk associated with PPI exposure in breast cancer patients. Treatment with PPIs was even included as a confounder for adjustment in the multivariate analysis of the risk of HF associated with ETs. The cardiovascular effects of PPIs have been reported before, but, to our knowledge, this is the first report in an oncology setting. Because this class of drugs was shown to delay the elimination of chemotherapy (918), PPIs could exert their cardiovascular effects both through intrinsic cardiotoxic properties and maintenance of cytotoxic drugs in the systemic circulation. Specific studies designed to characterize the cardiovascular risks associated with PPIs in breast cancer patients would be required to further explore this question.

6.4 The need to characterise the cardiovascular risks of antineoplastic agents

Although cytotoxic antibiotics of the anthracycline class are most strongly associated with cardiotoxicity (906), several innovative therapies can interfere with intracellular mechanisms of cardiac homeostasis leading to increased incidence of cardiovascular irregularities (945). Notably, the introduction trastuzumab as a systemic

treatment for Her-2 positive metastatic BC has highlighted the potential for unexpected cardiovascular effects of targeted therapies (555). Even if clinical trial data suggest that lapatinib may have a more favorable cardiotoxicity profile than trastuzumab (451), asymptomatic decline in the left ventricular ejection fraction has been recognised as a noteworthy side effect of Her-2 targeted BC therapies (305) (452). Many small molecule inhibitors targeting various effectors have been reported to affect the cardiovascular function of cancer patients (288). Epidermal growth factor receptor (EGFR) inhibitors, specifically cetuximab, erlotinib and panitumumab, have been associated with an increased risk of thromboembolism (946), whereas vascular endothelial growth factor (VGEF)-targeted agents were mostly associated with hypertension and congestive heart failure (947). Although several of these therapies are not formally indicated for the treatment of BC, many are used in an off-label context, as demonstrated in Chapter 5.

BC patients are at higher risk of developing multiple primary cancers (948) (949) (950) (951) and treatment utilized for BC may also impact the risk of secondary malignancies (952) (953). The development of secondary malignancies affects treatment decisions, but diagnosis of other malignancies is often listed as an exclusion criterion in clinical trials studies. Accordingly, the risks of adverse cardiovascular outcomes associated with different classes of antineoplastic therapy in this heterogeneous patient population have been poorly characterized.

The small number of exposed patients limited our ability to evaluate the risk associated with various drug combinations often used in the treatment of BC, as originally planned. Despite this limitation, preliminary analyses demonstrated an increase in the crude risk of HF following exposure to antineoplastic antibiotics, alkylating agents and antimitotic agents, with the highest level of risk observed with antineoplastic antibiotic treatment. These results are in line with the current literature on the cardiovascular disease risks associated with anthracyclines. Further analysis would be required to characterise the risk profiles of the sequential combination of chemotherapies and targeted agents to better inform treatment decisions in high risk patients.

6.5 The importance of off-label use in characterisation of cardiovascular risks

To date, most reports of cardiovascular outcomes stem from randomized clinical trials with controlled patient populations at low underlying cardiovascular disease risk who are prescribed a therapeutic regimen which may provide an inadequate representation of actual practice. In real-world clinical settings, off-label use of one or more drugs for a particular type or stage of cancer may be officially incorporated in recommendations from internationally renowned guidelines. For example, the anti-mitotic agent vinorelbine was

endorsed by the National Comprehensive Cancer Network (NCCN) for the treatment of recurrent or metastatic breast cancer (60). Our study presented in Chapter 6 confirms that what we define as breast cancer treatment should not be restricted to labelled indications. Of the 65 oncology drugs investigated, more than 55% were prescribed off-label and that most of the off-label encounters were evidence-based. We were able to identify factors relating to socio-demographic characteristics, insurance coverage, treatment center, and disease characteristics that appear to be associated with the off-label use. Because these unconventional breast cancer treatments have their own inherent safety profiles, a comprehensive approach, covering all antineoplastic agents administered, should be adopted in the evaluation of drug-induced adverse events.

Although clinical trials provide a good baseline reference point, the real-world risk is multifactorial and the cumulative effect of various pharmacotherapies may give rise to synergistic cardiovascular effects that are underreported in monotherapy studies. While there is a growing body of evidence and increased understanding of the pathogenesis of pharmacotherapy-induced cardiovascular dysfunctions, the process of determining how best to manage and prevent major cardiotoxicities remains a significant challenge. Oncologists, in collaboration with multidisciplinary teams, have the delicate responsibility of identifying the proper treatment combination that will maximize tumor response while minimizing adverse outcomes.

Conclusion

This thesis provides useful considerations for the prospective surveillance of the cardiovascular risks associated with estrogen-targeted therapies and other antineoplastic agents in breast cancer. Because patients are treated with a variety of therapeutic agents, including therapies that not formally indicated for the treatment of breast cancer, a comprehensive approach in the evaluation of the risk is needed to ensure that evidence-based decisions that will maximize tumor response while minimizing adverse outcomes. A multi-disciplinary approach should be adopted to facilitate the rapid diagnosis and treatment of cardiac complications secondary to cancer therapy.

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