Breast cancer risk associated with phosphate toxicity

by

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Author’s Declaration

This thesis consists of material all of which I authored or co-authored: see Statement of Contributions included in the thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Statement of Contributions

The three studies in this thesis have been published and are authored by Ronald B. Brown, in collaboration with co-authors and committee members. Exceptions to sole authorship include:

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As the corresponding author of the studies in Chapters 3 to 5, I was responsible for the conceptualization, methodology, investigation, writing the original draft, and preparing the final draft for submission to peer-reviewed journals. The co-authors reviewed and provided supervision during the research and provided feedback on the written manuscripts.

I also prepared other chapters of this thesis which were not included with the publications.

Abstract

Background

The essential dietary mineral phosphorus in the form of inorganic phosphate (PO_4^{3-}) is regulated in the blood serum by a sensitive network of endocrine hormones released from bone, kidneys, parathyroid glands, and intestines. Western dietary patterns are high in phosphorus-rich foods, including dairy, meats, grain products, and foods processed with phosphate additives. Consequently, average phosphate intake is far above the U.S. dietary reference intake of 700 mg for adults. Phosphate toxicity, the accumulation of excess inorganic phosphate throughout the body from dysregulated phosphate metabolism, is associated with tumorigenesis as high levels of inorganic phosphate within the tumor microenvironment stimulate cell signaling pathways and promote cancer cell proliferation. Breast cancer in women is projected to increase to 3-million new cases globally by 2040, yet much of the public remains unaware that breast cancer is associated with alcohol consumption, and phosphate toxicity may play a mediating role in the association of alcohol with breast cancer. Phosphate toxicity is also associated with osteolytic loss of bone mineral density and abnormal osteoblastic bone mineral deposition.

Methods

This thesis presents three studies investigating the association of phosphate toxicity with risk of breast cancer in women related to alcohol consumption, high dietary phosphate intake, and disorders of spinal bone mineral density. A grounded theory literature-review method was used in the first study to retrieve research findings from the literature on alcohol, kidney function, phosphate metabolism, rhabdomyolysis, and breast cancer. Findings were compared and categorized into concepts and themes and were synthesized into a theory positing a mechanism by which the association of breast cancer with alcohol consumption is mediated by phosphate toxicity.

The second study used a nested case-control design to measure the relative risk of breast cancer incidence associated with dietary phosphate intake levels in a cohort of middle-aged women from the Study of Women's Health Across the Nation. The lowest level of 800 to 1000 mg phosphorus per day, based on recommendations from the United States National Kidney Foundation, was used as the reference level to calculate the relative risk of breast cancer in the higher levels of phosphorus intake.

The third study used a mixed-methods grounded theory design to synthesize a theory relating phosphate toxicity with breast cancer and spinal bone mineral disorders. Based on the theory, the study used a mixed-effects model to test the hypothesis that changes in spinal bone mineral density are associated with incidence of breast cancer in women from the Study of Women's Health Across the Nation.

Results

Results of the first study found that alcohol burdens renal function, which can impair the regulation of inorganic phosphate, reduce excretion of excess serum phosphate, and increase phosphate toxicity, a potential mediating factor in breast cancer risk. Alcohol can also cause nontraumatic rhabdomyolysis which ruptures cell membranes and releases inorganic phosphate, contributing to hyperphosphatemia (blood serum phosphate levels above 4.5 mg/dL) with increased breast cancer risk. Furthermore, phosphate toxicity potentially mediates the risk of cancer associated with kidney disease in the medical specialty of onco-nephrology.

In the second study, the highest daily intake of dietary phosphorus in the cohort from the Study of Women's Health Across the Nation, >1800 mg, is approximately equivalent to menus promoted by the United States Department of Agriculture. This level of dietary phosphorus was associated with a 2.3-fold increase in the risk of breast cancer incidence compared to the reference level of 800 to 1000 mg (RR: 2.30, 95% CI: 0.94–5.61, $p = 0.07$). The study's clinically significant effect size, specificity, biological gradient, and other findings meet Bradford Hill's criteria for causative inference from epidemiological associations. Randomized trials are warranted to test epidemiological associations of dietary components with reduced risk of cancer, as recommended by the National Cancer Institute

The analysis of findings from the reviewed literature in the third study confirmed an association of phosphate toxicity with bone mineral disorders and tumorigenesis. In the follow-up study to test the hypothesis that bone mineral disorders are associated with tumorigenesis, women in the Study of Women's Health Across the Nation who self-reported breast cancer were found to have higher bone mineral density at baseline. But these women also had more rapid losses in bone mineral density during follow-up visits compared to women in the control group who remained cancer free. These findings are consistent with osteolytic and osteoblastic bone mineral changes associated with breast cancer.

Conclusions

Thesis findings provide the rationale for further clinical studies to test dietary phosphate as a modifiable cause of breast cancer and bone mineral disorders. The effect of alcohol associated with phosphate toxicity can also be disseminated to the public to increase awareness of the risk of breast cancer associated with alcohol consumption.

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List of Abbreviations

$1,25(OH)_2D_3$	Calcitriol
$25(OH)D_3$	Vitamin D3
AIC	Akaike Information Criterion
AICC	Akaike Information Criterion Corrected
AICR	American Institute for Cancer Research
Akt	protein kinase B
ATP	Adenosine Triphosphate
BIC	Bayesian Information Criterion
BMD	Bone Mineral Density
BRCA1 BRCA2	Breast Cancer Gene 1, 2
CI	Confidence Interval
CKD	Chronic Kidney Disease
CKD-MBD	Chronic Kidney Disease - Mineral Bone Disorder
CRF	Chronic Renal Failure
DCIS	Ductal Carcinoma in Situ
DEXA	Dual Energy X-ray Absorptiometry
DNA	Deoxyribonucleic Acid
DRI	Dietary Reference Intake
EAR	Estimated Average Requirement
eGFR	Estimated Glomerular Filtration Rate
FCS	Fully Conditional Specification Method
FFQ	Food Frequency Questionnaire
FGF23	Fibroblast Growth Factor 23
GT	Grounded Theory
HRT	Hormone Replacement Therapy
IARC	International Agency for Research on Cancer
IBC	Inflammatory Breast Cancer
IDC	Invasive Ductal Carcinoma
ILC	Invasive Lobular Cancer
IOM	Institute of Medicine
K/DOQI	Kidney Disease Outcomes Quality Initiative

LCIS	Lobular Carcinoma in Situ
LOCF	Last Observation Carry-Forward
MAR	Missing At Random
MI	Multiple Imputation
MM-GT	Mixed Methods-Grounded Theory
MRS	Magnetic Resonance Spectroscopy
mTOR	Mechanistic Target of Rapamycin Kinase
NaPi-IIb	Sodium Phosphate Cotransporter IIb
NCI	National Cancer Institute
NHANES	National Health and Nutrition Examination Survey
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NKF	National Kidney Foundation
P	Phosphorus
P53	Tumor Protein
Pi	Inorganic Phosphate
PI3K	phosphoinositide 3-kinase
PO_4	Phosphate
$PO4^{3-}$	Phosphate Anion
PTEN	Phosphatase and Tensin Homolog
PTH	Parathyroid Hormone
RDA	Recommended Dietary Allowance
RNA	Ribonucleic Acid
RR	Relative Risk
SWAN	Study of Women's Health Across the Nation
UL	Upper Intake Limit
USDA	United States Department of Agriculture
WHO	World Health Organization

Chapter 1.
Background

Background information in Chapter 1 covers the following sections: 1.1 Breast Cancer, 1.2 Phosphate Toxicity and Tumorigenesis, and 1.3 Grounded Theory and Knowledge Synthesis.

1.1 Breast Cancer

Female breast cancer incidence has replaced lung cancer as the most common type of cancer diagnosed across the globe, with 2.3 million new cases in 2020 reported in an analysis of GLOBOCAN statistics (1). Global incidence of breast cancer is predicted to continue to increase over the coming decades (2). Developing countries in Africa, Asia, and South America have faster rising incidence rates of breast cancer than fully developed countries, although incidence of breast cancer in developed Asian countries like Japan and the Republic of Korea is also rising quickly. Higher global prevalence of risk factors for breast cancer is attributed to lifestyle changes, increasing levels of excess body weight, and decreasing levels of physical activity. Importantly, the lack of programs for the primary prevention of breast cancer poses a significant challenge, and preventive efforts are needed to lower excess body weight, reduce alcohol consumption, and promote more physical activity.

The structure of the breast consists of glandular, fibrous, and fatty tissue attached to the anterior thoracic wall by Cooper's ligaments (3). The breast's specific function is to produce and secrete milk for lactation during breastfeeding, and breasts also play a role in female sexuality. Milk is produced in epithelial tissue of the breast which forms lobules, and the milk flows through ducts connected to the nipple, shown in Figure 1. The breast is also supplied with blood vessels, nerves, and lymphatics.

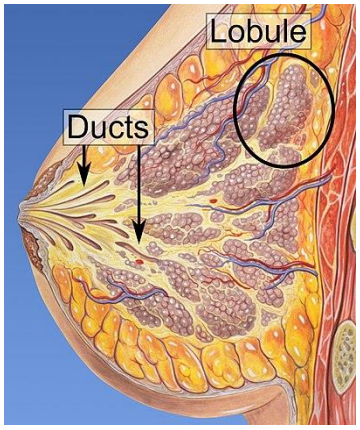

Figure 1. Lobules and ducts of the breast.

Courtesy Wikimedia Commons (4).

Specific cell differentiation in breast cancer determines the tumor type (5), and Table 1 lists the most common tumor types. Additionally, inherited breast cancer is linked to mutations in the *BRCA1* and *BRCA2* genes which affect about 3% (7,500) of annual U.S. breast cancer cases (6).

Table 1. Common breast cancer types.

National Breast Cancer Foundation (7).Ductal carcinoma in situ (DCIS)	Non-invasive cancer cells in the breast milk duct.
Invasive ductal carcinoma (IDC)	Most common (70–80%). Cancer cells spread from the milk duct to breast tissue.
Lobular carcinoma in situ (LCIS)	Non-invasive cancer cells in milk-producing lobules.
Invasive lobular cancer (ILC)	(10%) Cancer cells spread from lobules to breast tissue, blood, and lymph.
Triple negative breast cancer	Negative for hormone epidermal growth factor receptor 2 (HER-2), estrogen receptors (ER), and progesterone receptors (PR).
Inflammatory breast cancer (IBC)	Aggressive, skin inflammation, and cancer cells block lymph vessels.
Metastatic breast cancer	Stage 4 cancer spreads to other organs: lungs, bones, liver, and brain.

The recent history of breast cancer incidence shows that annual occurrence of the disease is relatively rare, with approximately two new cases occurring per year for every 1000 women in the United States in the 1980s (8). The incidence of breast cancer throughout the lifetime of women in the United States and Canada is currently about one out of every eight women, or approximately 13% (9, 10). The overall risk of a woman developing any type of cancer throughout her lifetime is 39.6% (11).

Annual incidence rates of breast cancer increased from the early 1980s until 2001, followed by a decrease that was attributed to reductions in screening and reduced use of hormone replacement therapy in menopausal women (12). By 2014–2018, annual incidence of female breast cancer in the United States had dropped to 1.29 new cases for every 1000 women, or 129.1 new cases per 100,000

women (13). Importantly, odds ratios of diseases like breast cancer with rare annual prevalence may be investigated with data from retrospective studies such as case-control studies. Moreover, case-control studies that are nested within cohorts provide longitudinal data to analyze associated risks of disease incidence (14), and a nested case-control study design was used in Study 2 and Study 3 of the present thesis.

Among controllable risk factors for cancer prevention, the World Cancer Research Fund/American Institute for Cancer Research recommends a diet that is high in fruits, vegetables, whole grains, legumes, and low in red meat with little processed meat, and other recommendations include reducing alcohol intake. (15). However, to meet the challenge of rising global incidence of breast cancer, more updated breast cancer research is needed in nutritional epidemiology, a branch of epidemiology that studies the association of diet and disease (16). For example, an early landmark study in nutritional epidemiology found that breast cancer mortality was significantly related to animal fat intake in many countries, according to an analysis by Carroll (17). Yet findings from cohort studies since then have been inconsistent (18), suggesting that other dietary factors may be involved: "we are not at a stage where we can justifiably advise women to reduce their fat intake to decrease the risk of developing breast cancer."

1.2 Phosphate Toxicity and Tumorigenesis

An understudied dietary factor that shows promise in the discovery of the cause and prevention of cancer is dietary phosphate. In 2018, inspired by Dr. Mohammed Razzaque's insights on phosphate toxicity, defined as excessive phosphate in tissues and cells of the body that harms most major organ systems (19), the present author and Dr. Razzaque coauthored one of the first comprehensive narrative reviews on tumorigenesis and phosphate toxicity (20).

The present thesis endeavors to advance nutritional epidemiological research by clarifying the role of dysregulated phosphate metabolism and phosphate toxicity as risk factors for breast cancer incidence. The dietary mineral phosphorus, often found in chemical combination with oxygen as phosphate (PO_4^{3-}), is an essential micronutrient with a dietary reference intake (DRI) of 700 mg/day for adults (21). Phosphorus is the second most abundant mineral in the human body next to calcium (22). Serum levels of inorganic phosphate (Pi) in adults normally range between 2.5 –4.5 mg/dL (23), and serum phosphate is regulated by endocrine hormones of a bone-kidney-parathyroid-intestine axis (24). Pi absorption in the intestines is regulated by bioactive vitamin D3 released by the kidneys,$1,25(OH)_2D_3$.

Fibroblast growth factor 23 (FGF23) released from bone and parathyroid hormone (PTH) released from the parathyroid glands inhibit kidney reabsorption of Pi and increase phosphaturia. PTH also increases resorption of calcium from bone. Excess calcium phosphate formed in the blood serum from dysregulated phosphate metabolism can lead to ectopic calcification deposited throughout soft tissue (25). Figure 2 shows the endocrine regulation of serum Pi.

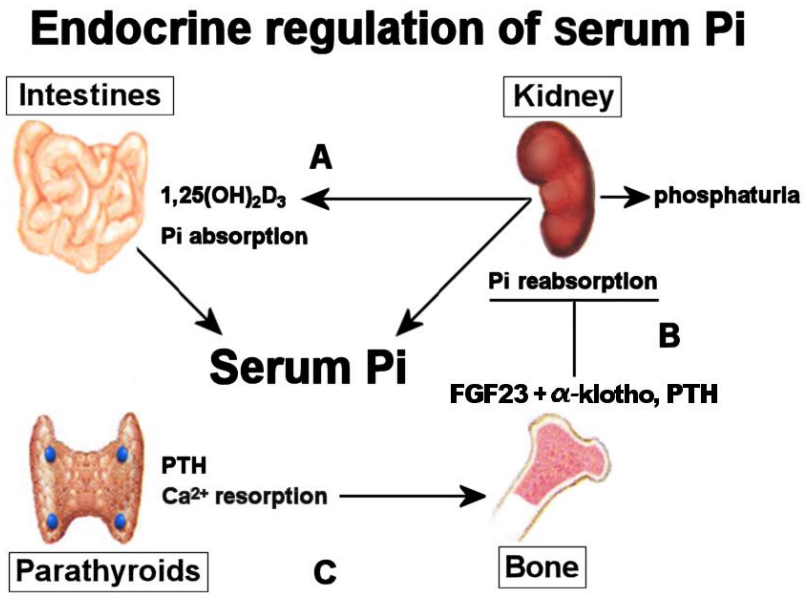

Figure 2. Endocrine regulation of serum Pi.

(A) Pi absorption in the intestines is increased by bioactive $1,25(OH)_2D_3$ released by the kidneys, which increases serum Pi. (B) FGF23 from bone and PTH from the parathyroid glands inhibit kidney reabsorption of Pi and increase phosphaturia. (C) PTH also increases resorption of calcium from bone. Additionally, α-klotho, a cofactor with FGF23, is released from the kidneys and the brain.As previously mentioned, phosphate toxicity from dysregulated phosphate metabolism is associated with tumorigenesis (20). Tissue levels of phosphate within mammals generally range between 0.5 and 5 mM, but in vitro experiments have shown that higher phosphate concentrations up to 10 mM can increase cell proliferation (26). Studies have shown that cell growth during tumor promotion is stimulated by uptake of excess phosphate into ribosomal RNA in cells (27). Epithelial and connective tissue, such as lacteal duct tissue in the breast, have storage properties that make them suitable for phosphate sequestration which stimulates tissue growth in tumorigenesis. Literature reviews confirm a strong association between risk of cancer incidence and dietary patterns that are high in phosphorus

(28). Dysregulation of phosphate metabolism is also associated with secondary hyperparathyroidism, kidney pathology, and bone mineral disorders such as osteoporosis (24, 25). Correspondingly, risk factors associated with breast cancer incidence also include bone mineral disorders (29), primary hyperparathyroidism associated with tumor growth (30), and kidney pathology (31). All of these conditions appear to share dysregulated phosphate metabolism as a common pathologic determinant, and more research is warranted in these areas.

Furthermore, animal studies have shown that high dietary phosphate stimulates the PI3K/Akt/mTOR signaling pathway and inactivates tumor suppression, increasing tumorigenesis (20) (Jin et al. 31). Figure 3 shows the cell signaling pathway used by high dietary phosphate to stimulate cancer cell growth. Note that kinases are enzymes that add phosphate groups to substrates, and phosphatases are enzymes that remove phosphate from substrates. High dietary phosphate activates a signaling pathway in which phosphoinositide 3-kinase (PI3K) phosphorylates Akt (protein kinase B) (32). Akt activates mTOR kinase, which suppresses cell apoptosis and upregulates protein synthesis and cell proliferation (33). High dietary phosphate was found to activate Akt phosphorylation, facilitating cap-dependent protein translation that increased lung tumorigenesis in mice (34). Furthermore, high dietary phosphate inactivated both PTEN (Phosphatase and Tensin Homolog), a tumor suppressor, and CTMP (Carboxy-Terminal Modulator Protein), a negative regulator of Akt activity.

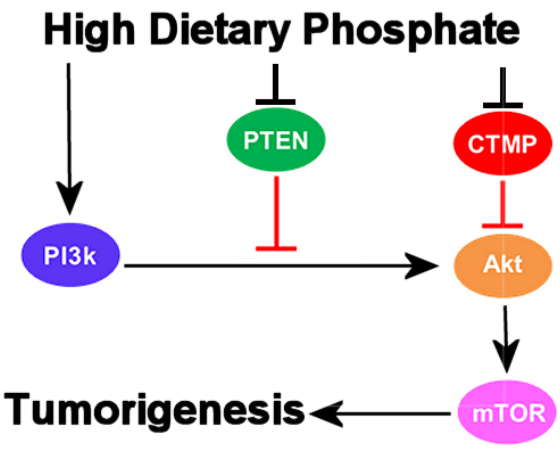

Figure 3. Phosphate and cancer cell signaling.

The overall aim of the present thesis is to integrate the latest research findings on phosphate toxicity, breast cancer, and related comorbid conditions, and synthesize a new research direction going forward that can meet the challenges of global breast cancer incidence.

1.3 Grounded Theory and Knowledge Synthesis

The grounded theory (GT) method used in the present thesis was originally developed in 1967 by sociologists Glaser and Strauss to bring a higher standard of quality and rigor to qualitative research (35). GT has also been utilized in quantitative research (35) and in Mixed Methods-Grounded Theory (MM-GT) (36). Using an iterative process of data collection and constant comparative analysis, GT enables researchers to construct a theory through induction, a method of discovering a principle from a set of data (35). However, unlike data collection in traditional GT, the grounded theory literature-review method in the present thesis uses published research findings as the source of data for synthesizing new knowledge (37), e.g., linking alcohol consumption with breast cancer, linking high dietary phosphate with breast cancer, and linking breast cancer with bone mineral disorders.

Purposeful sampling of information is based on sensitizing concepts, which guides selection of sources related to a subject that are rich in information and provide deeper understanding of the subject (38). Studies in the present thesis searched Google, Google Scholar, Pub Med, and Scopus using keywords including breast cancer, tumorigenesis, alcohol, dysregulated phosphate metabolism, phosphate toxicity. dietary phosphate, and bone mineral disorders. Additional keywords were obtained from retrieved studies as the trail of evidence was followed, and all data sources relevant to the subject were considered without restrictions on date, type, or number of sources.

Pathophysiological mechanisms and epidemiological concepts obtained from research findings on breast cancer and phosphate toxicity were sorted into categories and themes through comparative analysis. Themes were synthesized into causative, associative, and mediating epidemiological relationships (39). Directed acyclic graphs were created to illustrate the associated and causative relationships of concepts and themes (40, 41). As the theory began to emerge, additional data were collected through theoretical sampling to fill in knowledge gaps (35). Data collection continued until theoretical saturation was reached, the point where new knowledge was no longer obtained through analysis.

The Canadian Institutes of Health Research defined knowledge synthesis as “the contextualization and integration of research findings of individual research studies within the larger body of

knowledge on the topic. A synthesis must be reproducible and transparent in its methods, using quantitative and/or qualitative methods" (42). Synthesized knowledge addresses gaps and controversies in the research literature and contributes new insights and future directions for further study (39). Grounded theory researchers begin an investigation with a clean slate, without assumptions, and use an iterative process of comparative analysis of the data to inductively construct a novel theory. The researcher can then develop testable hypotheses deducted from the grounded theory. The strengths and weaknesses of linked concepts can strengthen or weaken a synthesis of new knowledge. The following text from the present author's "Breakthrough Knowledge synthesis in the Age of Google" (39) summarizes the strengths and limitations of four types of linked relationships used throughout the studies in the present thesis: association, causation, mediation, and transitive inference. Understanding these relationships will assist the reader in following the logic behind the research methods, results, discussions, and conclusions of the three studies in the thesis.

Association: When associating concepts in a synthesis, the aim is to form a relationship in which the variables are meaningfully linked together—i.e., as one variable changes, another variable also changes to some extent. The limit of associative relationships is that they cannot demonstrate causation, and it is sometimes difficult to identify spurious associations that are related only by chance.

Causation: A causative relationship is one in which an independent variable is proven to directly cause an effect on a dependent variable or outcome. The highest form of evidence demonstrating causation is from a randomized controlled trial, but clinical trials are not always feasible in research settings. Bradford Hill suggested criteria for inferring causation from observational evidence in epidemiology studies, which includes the strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment evidence, and analogy (43).

Mediation: A mediator is a variable that forms an indirect causative pathway between two other variables. A directed acyclic graphic, shown in Figure 4, from Baron and Kenny (41) is used throughout the present study to visually represent a mediated causal pathway between an independent variable and outcome variable (40).

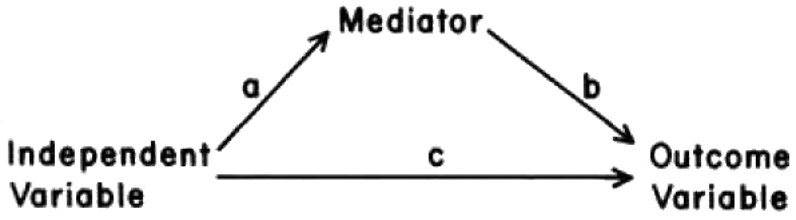

Figure 4. Directed acyclic graph of a mediated causative pathway between variables.

From Baron and Kenny (41)**.**

Confounders and effect modifiers lie outside the causation pathway (41). A confounding variable is an additional independent variable that is linked to the same outcome variable, but through a separate causative pathway. Modifiers such as age, ethnicity, etc. change the effect of the outcome variable caused by the independent variable. For example, if phosphate toxicity mediates the effect of alcohol consumption with breast cancer, other variables like age, sex, health status, ethnicity, etc. may moderate the outcome. When selecting information during knowledge synthesis, conflicting findings in the literature help identify areas requiring further in-depth investigation, leading to the potential discovery of mediating factors that may resolve the conflict.

Transitive inference: Similar to the manner in which mediation extends the number of variables indirectly linked in a causative pathway, transitive inference extends the number of variables indirectly linked in associative pathways, as used in *literature-based discovery*, a synthesis method in which implicit knowledge is discovered from associating separate bodies of literature (44). For example, if concept A is related to concept B in one body of literature, and a separate body of literature relates the same concept B to concept C, transitive inference is used to indirectly link A from one body of literature to C in another body of literature. Although not proving causation, transitive inference is a very powerful exploratory method to help develop novel transdisciplinary theories and investigate gaps and controversies in the research literature.

Chapter 2.
Study Rationale and Objectives

Study 1 questions the mechanisms by which alcohol consumption is associated with breast cancer. A literature review in Study 1 describes how most women are unaware that alcohol consumption is associated with increased risk of breast cancer incidence in a dose-dependent manner (45). Although World Health Organization's International Agency for Research on Cancer declared alcoholic beverages carcinogenic (46), an exact causative mechanism remains unclear. Laboratory animals fed solutions of ethanol developed a variety of adenomas in glandular tissue and carcinomas in epithelial tissue in a dose-dependent manner, but ethanol *per se* was not found to be carcinogenic (47). Additionally, breast cancer cells and cancer cells have been shown to store high levels of inorganic phosphate (20, 48-53). However, no studies in the research literature have examined a potential link between phosphate toxicity, breast cancer, and alcohol consumption.

Findings from the research literature in Study 1 provide the rationale to hypothesize that a novel biomechanism involving phosphate toxicity mediates the association of alcohol intake with breast cancer risk. The objective of the study is to construct a grounded theory that describes specific mechanisms by which phosphate toxicity potentially mediates the association of alcohol intake with breast cancer.

Study 2 questions if high dietary phosphate intake is associated with increased breast cancer risk. A literature review in Study 2 found that increased mortality in a U.S. population was associated with high dietary phosphorus intake starting at approximately 1400 mg per day (54). Furthermore, a MyPlate 2000-calorie daily menu recommended by the U.S. Department of Agriculture, including whole grains and fat-free milk, contained well above the 1400 mg phosphorus level associated with increased mortality risk, with approximately 1800 mg phosphorous (55).

The literature review in Study 2 also shows that high dietary phosphate intake causes tumors in animals (34, 56), and that, as previously mentioned, cancer cells in humans are high in phosphate. These findings provide the rationale to hypothesize that high dietary phosphate in middle-aged women is associated with increased risk of breast cancer incidence. The objective of the study is to analyze data from a cohort of middle-aged women, the Study of Women's Health Across the Nation (57), to determine the relative risk of breast cancer incidence associated with high dietary phosphate

intake compared to lower dietary phosphate intake. Study 3 questions the mechanisms by which phosphate toxicity affects bone mineral density in breast cancer. In addition to the previous described association of excessive phosphate with tumorigenesis, a literature review in Study 3 also describes an association of phosphate toxicity with abnormal bone mineral density in bone mineral disorders (25, 58, 59). Furthermore, osteolytic changes or loss of healthy bone in cancer are often combined with osteoblastic changes, gain of unhealthy bone deposits (60). The common factor of phosphate toxicity shared by tumorigenesis and bone mineral disorders provides the rationale to hypothesizes that phosphate toxicity mediates an association of breast cancer with osteolytic and osteoblastic changes in bone mineral density.

Study 3 is a mixed methods-grounded theory study. The objective in the qualitative portion of Study 3 is to construct a grounded theory positing that phosphate toxicity mediates bone mineral density changes associated with breast cancer incidence. The objective in the quantitative portion of the study is to analyze data in a cohort of middle-aged women, the Study of Women's Health Across the Nation (57), to investigate breast cancer incidence with longitudinal changes in bone mineral density using a linear mixed-effects model.

Chapter 3.

Study 1. “Breast cancer, alcohol, and phosphate toxicity”

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3.1 Abstract

Alcohol consumption is associated with an increased risk of breast cancer, even at low alcohol intake levels, but public awareness of the breast cancer risk associated with alcohol intake is low. Furthermore, the causative mechanisms underlying alcohol's association with breast cancer are unknown. The present theoretical paper uses a modified grounded theory method to review the research literature and propose that alcohol's association with breast cancer is mediated by phosphate toxicity, the accumulation of excess inorganic phosphate in body tissue. Serum levels of inorganic phosphate are regulated through a network of hormones released from the bone, kidneys, parathyroid glands, and intestines. Alcohol burdens renal function, which may disturb the regulation of inorganic phosphate, impair phosphate excretion, and increase phosphate toxicity. In addition to causing cellular dehydration, alcohol is an etiologic factor in nontraumatic rhabdomyolysis, which ruptures cell membranes and releases inorganic phosphate into the serum, leading to hyperphosphatemia. Phosphate toxicity is also associated with tumorigenesis, as high levels of inorganic phosphate within the tumor microenvironment activate cell signaling pathways and promote cancer cell growth. Furthermore, phosphate toxicity potentially links cancer and kidney disease in onco-nephrology. Insights into the mediating role of phosphate toxicity may lead to future research and interventions that raise public health awareness of breast cancer risk and alcohol consumption.

3.2 Introduction

Fewer than half of the people responding to a 2019 survey on cancer awareness conducted by the American Institute for Cancer Research (AICR) were aware that cancer was linked to alcohol consumption (61). The AICR suggested that popular messages about alcohol's benefits for heart health may distract people from warnings that alcoholic beverages—beer, liquor, and wine—are a "clear and convincing cause of several cancers, including breast and liver cancers." Another recent survey found that less than 20% of women in breast screening programs knew that alcohol consumption is a modifiable risk factor for breast cancer (45).

According to the World Health Organization (WHO),

> "Many people, including women, are not aware that breast cancer is the most common cancer caused by alcohol among women globally"(62).

Furthermore, due to alcohol's toxic effect in every organ as it passes through the body, WHO warned that there is no safe level of alcohol consumption, and WHO stated that the risk of breast cancer increases with each unit of alcohol consumed per day (62). Findings of a recent national survey of U.S. adults highlighted "the need to educate U.S. adults about the alcohol-cancer link, including raising awareness that drinking all alcoholic beverage types increases cancer risk" (63). Yet, specific pathophysiological mechanisms linking alcohol with cancer are under-investigated.

Global cancer incidence related to alcohol consumption was estimated from an analysis of GLOBOCAN 2020 data by WHO's International Agency for Research on Cancer (IARC) (64). Cancer attributed to alcohol consumption accounted for 4.1% of all new cancer cases globally in 2020. At 10 g of alcohol per drink, daily alcohol consumption was classified as moderate, <20 g, risky, 20-60 g, and heavy, >60 g. Heavy, risky, and moderate consumption of alcohol accounted for 46.7%, 39.4%, and 13.9% of new cancer cases, respectively. Lighter consumption of alcohol—up to 10 g a day—accounted for 41,300 new cancer cases. Furthermore, among potentially modifiable risk factors associated with incidence of U.S. cancer cases and deaths in 2014, alcohol intake ranked just behind cigarette smoking and excess body weight, accounting for 5.6% of cancer cases and 4% of cancer deaths (65).

A 2020 study from the U.S. National Institute on Alcohol Abuse and Alcoholism (NIAAA) reported that alcohol use is increasing in U.S. adult women but not in men—64% of females consume alcohol

compared to 68% of males (66). Although women consume less overall alcohol than men, women are at greater risk from harm due to lower levels of body weight and body water, which increase women's susceptibility to toxic effects from higher concentrations of blood alcohol. Breast cancer is among cancers associated with light alcohol consumption (67). A review by Soccianti et al. cited eight cohort studies and six case-control studies showing a dose-dependent linear relationship between increasing alcohol intake and female breast cancer risk (68). For each additional beverage consumed containing approximately 10 to 12 grams of alcohol, a statistically significance increase in the relative risk of breast cancer was shown, ranging from 2% (relative risk: 1.02, 95% CI: 101, 103) to 12% (relative risk: 1.12, 95% CI: 1.09, 1.14) (69-71). *Dietary Guidelines for Americans: 2020-2025* defines heavy alcohol drinking for women as four or more drinks in one day or eight drinks in one week (72). Of concern, a survey during the COVID-19 pandemic found a 41% increase in alcohol consumption by U.S. women, which may be related to increased anxiety and depression (73). Furthermore, recurrence of breast cancer is associated with alcohol consumption, including low consumption levels, especially in postmenopausal women (74).

Relatedly, phosphate toxicity, the damaging effect on organ systems from accumulation of dysregulated inorganic phosphate in the body, has been associated with tumorigenesis, and cancer cells have been shown to store high levels of inorganic phosphate (20, 48-53). This evidence provides a very strong rationale to further investigate phosphorus in Chapter 3. Phosphate is normally regulated by the kidneys and other organs through a network of endocrine hormones (Section 3.4), but when kidney function is burdened, excessive amounts of inorganic phosphate can accumulate in the tumor microenvironment and stimulate cancer cell growth through cell-signaling pathways (Section 3.7). However, no studies in the research literature have examined a potential mechanism linking phosphate toxicity, breast cancer, and alcohol consumption.

Current hypotheses of cancer-causing mechanisms include ethanol's impairment of tumor cell destruction by natural killer cells, activation of cell proliferation related to estrogen, and carcinogenic effects of alcohol metabolites such as acetaldehyde and oxygen reactive species (64, 75). Yet none of these hypotheses have proven how alcohol consumption causes breast cancer.

Among possible nutritional risk factors for breast cancer, The National Cancer Institute noted that numerous studies have investigated individual nutrients or dietary components associated with changes in cancer risk, but that no randomized clinical trial has yet demonstrated a change in cancer

risk caused by a specific nutrient (76). Few nutrients in reviews of the research literature are strongly associated with cancer, and causative evidence is lacking or is inconsistent (77, 78). A notable exception among nutrients related to cancer risk is excessive levels of phosphorus. For example, a 2023 review on the association of breast cancer and diet included a wide selection of diet-related metabolites, including metabolites from protein, fat, and carbohydrates. The authors found no conclusive evidence that specific diet-related metabolites cause or prevent cancer, yet inorganic phosphate, a metabolite of dietary phosphate, was noticeably absent from the review (79).

Other dietary factors strongly associated with cancer, like obesity and ultra-processed food consumption, are potentially mediated by increased dietary phosphate intake, especially in the form of phosphate additives (80). Plant-based dietary patterns are also strongly associated with cancer protection and are generally lower in phosphate compared to conventional Western dietary patterns (81). Based on the totality of studies finding that other nutritional and biochemical factors related to alcohol consumption do not directly cause breast cancer, the present study proposes that excessive phosphorus and phosphate toxicity are plausible nutritional and biochemical factors that mediate the association of alcohol consumption with breast cancer.

3.3 Method

The present theoretical paper used a "Grounded Theory Literature-Review Method" proposed by Wolfswinkel et al. (37) to rigorously and objectively select and analyze findings from the research literature in the investigation of phosphate toxicity, breast cancer, and alcohol. Detailed descriptions of the grounded theory literature-review method and knowledge synthesis are provided in Chapter 1.3. A unique difference between reviewing the literature with grounded theory in contrast to a conventional narrative review is that grounded theory synthesizes new knowledge from a comparative analysis of findings from the literature using induction—a method of discovering a principle from a set of data (35). The data in a grounded theory literature-review are the findings from the reviewed literature. Theoretical sampling is further used to select and analyze additional data from the literature to fill in gaps in the developing theory. (35).

Beginning with purposeful sampling, which selects sources rich in information for deeper understanding of an unknown subject (38), the present study searched Google, Google Scholar, Pub Med, and Scopus using keywords including breast cancer, alcohol, dysregulated phosphate metabolism, and phosphate toxicity. Additional keywords were obtained from retrieved studies as the

trail of evidence was followed, and all data sources relevant to the subject were considered without restrictions on date, type, or number of sources.

The grounded theory proposed in the present paper introduces a novel mechanism by which phosphate toxicity mediates the association of alcohol consumption with increased breast cancer incidence. Insights and perspectives from this grounded theory may inform hypotheses for further research and help raise awareness of breast cancer risk associated with alcohol.

3.4 Endocrine Regulation of Phosphate

A detailed explanation of the endocrine regulation of phosphate is in Chapter 1.2. Serum inorganic phosphate (Pi) is regulated by endocrine hormones from bone, the kidneys, parathyroid glands, and intestines (24). Pi absorption in the intestines is increased by kidney activation of vitamin D3, 1,25-dihydroxyvitamin D. Fibroblast growth factor 23 and parathyroid hormone increase phosphaturia, and parathyroid hormone resorbs calcium from bone Factors that reduce renal function can contribute to dysregulated phosphate metabolism and cause an abnormal rise of serum Pi levels in hyperphosphatemia. The following sections explain how alcohol burdens kidney function and causes nontraumatic rhabdomyolysis, leading to high serum levels of dysregulated Pi associated with increased risk of breast cancer.

3.5 Alcohol Carcinogenicity and Dysregulated Phosphate

A Monograph Working Group of the IARC in 2007 declared that alcoholic beverages were carcinogenic (46), although the exact causative mechanisms remain unclear. More than a dozen studies reviewed by the IARC (47) have shown that laboratory animals fed solutions of ethanol developed a variety of adenomas and carcinomas in a dose-dependent manner (82-96).

Current hypotheses of cancer-causing mechanisms include ethanol's impairment of tumor cell destruction by natural killer cells, activation of cell proliferation related to estrogen, and carcinogenic effects of alcohol metabolites such as acetaldehyde and oxygen reactive species (64, 75). Acetaldehyde, which is metabolized from ethanol in alcoholic beverages, damages DNA (97). Acetaldehyde is converted into the less toxic form of acetate by the liver through the enzymatic action of aldehyde dehydrogenase 1, but triple-negative breast cancer patients with lower genetic expression of this enzyme were found to have poorer prognosis associated with acetaldehyde accumulation from alcohol consumption (98). Alcohol has been implicated in raising female hormone levels, thus

increasing risk for hormone-related cancers (99). However, the effect of alcohol does not appear to directly increase biosynthesis of the major female hormone estradiol—rather, due to enzymatic degradation of alcohol, estradiol's breakdown to estrone is reduced, allowing estradiol levels to rise. An increase in serum levels of steroid hormones from alcohol intake, including dehydroepiandrosterone sulfate, was also associated with breast cancer in postmenopausal women (100), and other androgens from alcohol intake are associated with breast cancer (101).

Consumption of alcohol also burdens immune system function which contributes to the initiation and promotion of breast cancer (102). Cancer cell proliferation and metastasis is also promoted by oxidative stress and inflammation associated with chronic consumption of alcohol (103). However, the growth rate hypothesis developed by Elser et al. in 1996 (104) posits that phosphorus is a growth-rate limiting factor in protein biosynthesis (105), implying that growth-promoting hormones, carcinogens, oxidative stress, and inflammation associated with alcohol intake require a sufficient supply of phosphorus to promote breast cancer-cell growth.

Ironically, ethanol is also used therapeutically to dehydrate, rupture, and kill cancer cells in human patients through percutaneous injections into the liver (106), implying that alcohol's carcinogenic action may be indirect and mediated by other factors. Additionally, alcohol's harmful effects can cause kidney injury (107), and dehydration from alcohol burdens the kidneys' ability to filter blood and maintain fluid and electrolyte balance (108), which can contribute to dysregulated serum Pi.

Because serum concentrations of calcitriol and 25(OH)D3 are reduced in people with alcoholism, researchers hypothesized that alcohol could interfere with biosynthesis of calcitriol in breast tumor cells, which is enzymatically increased by 25(OH)D-1α-hydroxylase expressed by gene CYP27B1, and decreased by 1,25-dihydroxyvitaminD-24 hydroxylase, expressed by CYP24A1 (75). Moderate chronic ethanol intake in a murine model was found to increase tumor cell CYP24A1 and decrease renal CYP27B1, suggesting reduced renal biosynthesis of calcitriol from 25(OH)D3, and degradation of both 25(OH)D3 and calcitriol in breast cancer cells. In support of potential mediation by phosphate toxicity in alcohol-related breast cancer, hyperphosphatemia-induced release of FGF23 and its cofactor α-klotho (109) suppress CYP27B1 and induce CYP24A1 expression to "inhibit the synthesis and promote the catabolism" of calcitriol (110).

3.6 Alcohol, Rhabdomyolysis, Hyperphosphatemia, and Phosphate Toxicity

In rhabdomyolysis, skeletal muscle ruptures and intracellular phosphate compounds break apart, releasing excessive amounts of Pi into serum causing hyperphosphatemia (111). A key finding in the literature is that rhabdomyolysis is most often caused by exposure to drugs and toxins (111), and alcohol is a non-exertional, nontraumatic etiological factor in rhabdomyolysis (112), which implies an indirect association of alcohol with hyperphosphatemia and phosphate toxicity. Other intracellular components released from damaged muscle cells include myoglobin and creatine phosphokinase, which can disturb the balance of serum electrolytes like calcium and phosphate. Relatedly, between 30–40% of rhabdomyolysis cases develop acute kidney injury (112), potentially associated with excessive serum Pi levels. Additionally, rhabdomyolysis is associated with polymyositis, an inflammatory condition of muscle that has been linked to increased incidence of breast cancer (113), which may be related to phosphate toxicity that causes inflammatory damage to muscle cells (114).

A large number of cancer cell deaths that occur during cancer treatment can cause tumor lysis syndrome, in which tumor cells release their intracellular contents into the blood, raise levels of serum Pi and other electrolytes, and can increase kidney injury and failure (115). A review of rhabdomyolysis for clinical practice in acute kidney injury noted pathophysiologic similarities with tumor lysis syndrome (116). Of relevance, incidence of secondary sarcomas was higher in patients treated with radiation, surgery, and chemotherapy than with surgery alone, which could be related to dysregulated levels of phosphate released during tumor lysis from radiation and chemotherapy (117). A low-phosphate diet in patients receiving radiation and chemotherapy might help mitigate the risk of phosphate toxicity from tumor lysis syndrome, but more studies are needed in this area.

According to the National Kidney Foundation, "Regular heavy drinking has been found to double the risk [of] chronic kidney disease, which does not go away over time" (118). Although uncommon, cases have been reported of nontraumatic rhabdomyolysis associated with a history of short-term alcohol intoxication (119, 120). Alcohol-induced rhabdomyolysis is also associated with inhibition of calcium transport in the sarcoplasmic reticulum of cardiac muscle (121), possibly related to inhibition of ATP hydrolysis due to rising concentrations of the Pi end product (122). Cardiac disturbance in "Holiday Heart," paroxysmal atrial fibrillation, is also more frequent when people increase alcohol consumption during the annual holiday season, even with moderate drinking (123). Importantly, less severe rhabdomyolysis raises serum creatine kinase but is asymptomatic (124), inferring that the

association of breast cancer risk with light to moderate drinking may be linked to lower levels of rhabdomyolysis severity. More studies are needed to investigate associations of rhabdomyolysis severity with different levels of alcohol exposure. Research should also examine the chronic effect of small amounts of phosphate released into serum from asymptomatic, nontraumatic rhabdomyolysis associated with lower alcohol consumption, which is a plausible mechanism potentially linking breast cancer with light drinking over long periods.

Relatedly, exposure to alcohol in the human body occurs not only through consumption, but also through inhalation and dermal contact. Prajapati et al. reported that acute exposure to ethanol disinfectants is non-toxic, "however, blood ethanol levels are affected with long-term exposures to ethanol-based hand sanitizers," which is more likely to have been an issue during the COVID-19 pandemic (125). Ethanol from hand sanitizers can also enter the body through inhalation of ethanol vapor (126). Health Canada issued warnings that acetaldehyde from ethanol-based hand sanitizers raises concerns about potential carcinogenicity, especially with long duration of use (127).

In addition to rhabdomyolysis, other mechanisms related to alcohol exposure may contribute to carcinogenesis. Aqueous-organic solvents containing alcohol significantly increase solubility of hydrophobic compounds in toxic waste (128), implying increased exposure to hazardous and possibly carcinogenic environmental pollutants when coming into contact with these alcohol compounds.

In summary, alcohol contributes to renal burden which may increase dysregulated phosphate. Alcohol also causes nontraumatic rhabdomyolysis which increases serum Pi and potentially leads to hyperphosphatemia and phosphate toxicity. Furthermore, rhabdomyolysis is indirectly linked with breast cancer in polymyositis and produces pathophysiologic effects similar to tumor lysis syndrome, which may occur in milder forms with recurrent low exposure to alcohol.

3.7 Breast Cancer and Phosphate Toxicity

Cancer in adults is associated with hyperphosphatemia (129, 130), except for reproductive cancers in females, possibly due to a shift of serum phosphate into reproductive tissue under the mitogenic effect (cell proliferation) of estrogen. Of relevance, phosphate toxicity can occur in cells even if serum Pi levels are normal (131), and further studies should examine phosphate shift in reproductive cancers.

In support of higher phosphate needs for female reproduction functions, a study of lactating women found elevated mean serum phosphate levels and lower PTH levels compared to controls (132).

Additionally, intestinal phosphate absorption doubles in pregnancy as serum calcitriol levels rise (133). Furthermore, breast milk contains phosphorus, and researchers using P-31 MRS suggested that higher levels of the phosphate metabolite phosphomonoester found in the lactating breast were related to the higher proportion of milk-producing epithelial tissue in the breast lobules (134). Increased phosphate demand during pregnancy and lactation might lower breast cancer risk associated with dysregulated Pi, and only 3% of women develop breast cancer while breastfeeding (135). Breast cancer risk also drops by 4.3% for every 12 months of breastfeeding (136).

Excessive cell growth during tumor promotion and progression is stimulated by uptake of excess Pi into ribosomal RNA in cells (27). Epithelial tissue, such as lacteal duct tissue in the breast, has storage properties suitable for phosphate sequestration and growth of carcinomas, such as invasive ductal carcinoma which accounts for approximately 80% of breast cancers (137). Compared to normal tissue, breast carcinomas had a higher and faster uptake of phosphorus isotope P32 with longer retention (138), and mean Pi levels in breast cancer tissue were more than three-fold higher than normal tissue (139).

Earlier studies of breast cancer using P-31 magnetic resonance spectroscopy (MRS) found lower levels of inorganic phosphate, adenosine triphosphate (ATP), and other phosphate metabolites in normal breast tissue compared to breast tumors (140-144). Furthermore, the sodium phosphate cotransporter NaPi-IIb (*SLC34A2*) is highly expressed in breast cancer (52, 145). However, H^+-dependent phosphate transporters in breast cancer cells were recently found to increase Pi uptake by five-fold compared to sodium phosphate cotransporters, which researchers suggested occurs when sodium phosphate cotransporters become saturated with increasing concentrations of Pi in the tumor microenvironment (51).

Cell signaling in tumorigenesis is also activated by high levels of Pi (32), and tumor neovascularization is stimulated as well (146). Additionally, high Pi levels are associated with chromosome instability (147) and Pi levels measured in extracellular tissue are associated with metastatic cancer progression (148). Schipper et al. (149) proposed that dysregulated metabolic pathways linked to cancer promotion may be reversible, implying that dietary phosphate modification may reduce cancer risk. A review of research literature suggests a strong association between risk of cancer incidence and dietary patterns that are high in phosphorus (28).

3.8 Onco-nephrology and Dysregulated Phosphate

This section provides additional evidence supporting the association of phosphate toxicity with breast cancer. Dysregulation of phosphate metabolism is associated with kidney pathology (24, 25), and kidney pathology is among the risk factors associated with breast cancer (31). Thus, breast cancer and kidney disease potentially share dysregulated phosphate metabolism as a common pathophysiological determinant. Chronic kidney disease is so strongly associated with cancer that a transdisciplinary medical specialty evolved to study a link between nephrology and oncology, onco-nephrology (150, 151). Prevalence of chronic kidney disease at time of cancer diagnosis was reported as 12–53%, and glomerular filtration was reduced in 50–60% of cancer patients (GFR< 90 mL/min/1.73 m^2) (152), leading to recommendations for a comprehensive onco-nephrological examination in cancer patients to evaluate disturbances in electrolytes, including phosphate.

Kidney vulnerability to nephrotoxic injury is increased from exposure to exogenous toxins and drugs (153). Dysregulated metabolism and electrolyte disorders also increase patient vulnerability to renal toxicity, and a significant number of patients are also vulnerable to chronic kidney disease caused by phosphate nephropathy. Note that hypophosphatemia also commonly occurs in cancer patients as a serious complication. Hypophosphatemia is associated with various conditions such as malnutrition from inadequate dietary phosphate intake, adverse therapy effects of chemotherapy drugs, critical illness with poor intestinal phosphate absorption, or a large transcellular Pi shift, including rapid Pi absorption by growing malignancies in tumor genesis syndrome (154).

Researchers in onco-nephrology are studying kidney disease and electrolyte/acid-base disturbances as complications in cancer biology and as effects of treatments for cancer (155). Chronic kidney disease and acute kidney injury (AKI) are highly prevalent in cancer patients and can be severe. “Cancer-related metabolic disturbances” and “tissue deposition of paraproteins” in cancer are associated with risk of AKI. Patients with glomerulopathy have a higher risk of cancer than the general population, and cancer mortality is highest in patients requiring dialysis for AKI. Patient survival is also very poor in cancer-associated hypercalcemia, which is often caused by release of parathyroid hormone.

An excessive risk of cancer has been identified in patients with early stages of chronic kidney disease (CKD), defined by the National Kidney Foundation Kidney Disease Outcome Quality Initiative as either kidney damage or an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 for >3 months (156). Advanced stages of chronic kidney disease, stages 3-5 in women diagnosed with breast

cancer, are associated with increased risk of mortality, regardless if the women received chemotherapy or radiotherapy (157).

Among women with breast cancer, an eGFR < 60 mL/min/1.73 m^2, compared to no eGFR reductions, was associated with a 2- to 2.5-fold increased risk of breast cancer mortality in a model adjusted for most known risk factors of cancer death (158). The researchers implied that increased cancer mortality risk associated with a lower eGFR could be related to exposure to higher serum levels of uremic toxins, but the precise biological mechanism was not clear and was likely multifactorial. By contrast, a meta-analysis found no statistically significant association between reduced renal function in chronic kidney disease patients and overall risk of cancer, likely because the authors acknowledged that "our study did not have sufficient power to exclude an increase in risk of particular cancers among patients with less severe renal impairment"(159). However, relative to patients in the meta-analysis with higher eGFR, dialysis patients had an increase in cancer deaths and increased incidence of endocrine, urinary tract, and digestive tract cancers.

Although excess phosphate in breast tissue may not directly attract other toxins into the breast, excessive accumulation of Pi, considered a uremic toxin by some researchers, is associated with more than 153 other uremic toxins originating from impaired renal function (160). Uremic patients were found to have persistently high serum levels of carcinogenic compounds, which is associated with increased incidence of cancer in patients with chronic renal failure (161). Women with CKD have an increased risk of mortality from breast cancer related to release of proinflammatory cytokines (162), which is stimulated by uremic toxins, primarily indoxyl sulfate, p-cresyl sulfate, and indole-3-acetic acid (163).

Other conditions associated with dysregulated phosphate metabolism include ectopic calcification, hyperparathyroidism, and low levels of vitamin D—and each condition is associated with breast cancer, thereby indirectly linking breast cancer with phosphate toxicity. For example, microcalcification clusters in mammograms were an independent risk factor associated with breast cancer in a cohort of Swedish women (164). Primary hyperparathyroidism shares characteristics in common with breast cancer, suggesting "common etiological pathways"(165). Up to 30% to 40% of patients diagnosed with non-aggressive breast cancer have an occurrence of hypercalcemia, potentially caused by primary hyperparathyroidism from parathyroid gland hyperplasia or an adenoma. Even 15 years after parathyroidectomy, risk of malignancy persists, "suggesting genetic

predisposition or environmental factors as causal mechanisms, rather than biochemical changes"(166). Many studies have also found an inverse association between risk of breast cancer and serum levels of 25(OH)D3 (167), and calcitriol is inversely associated with cancer cell growth (168).

3.9 Grounded Theory: Alcohol and Breast Cancer Mediation by Phosphate Toxicity

Based on analysis of evidence from published research findings, the grounded theory in the present theoretical paper proposes that the association of alcohol consumption with risk of breast cancer is mediated by phosphate toxicity. A hypothetical causative pathway is illustrated in the directed acyclic graph in Figure 3. Alcohol consumed in a dose-dependent manner in women, even at low levels, can induce renal burden which compromises Pi regulation. Alcohol also causes nontraumatic rhabdomyolysis which ruptures skeletal cell membranes, releasing excessive intracellular phosphate into the blood serum, increasing hyperphosphatemia and risk of phosphate toxicity. Tumorigenesis is also associated with phosphate toxicity. Thus, phosphate toxicity is proposed to mediate the association of alcohol consumption with increased breast cancer incidence.

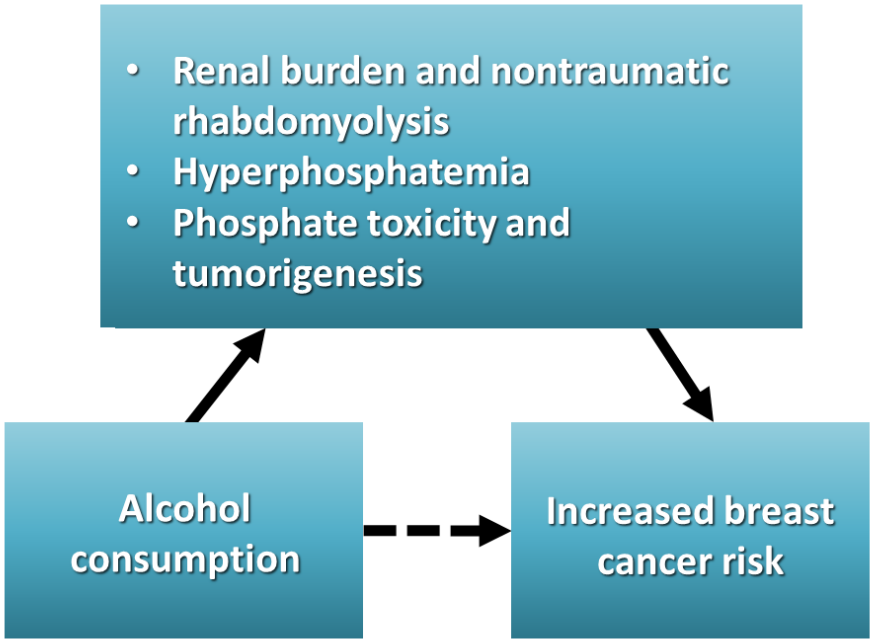

Figure 5. The link between alcohol and increased breast cancer risk.

Mediation by alcohol-induced renal burden and nontraumatic rhabdomyolysis, leading to hyperphosphatemia and phosphate toxicity associated with tumorigenesis.

Conclusions

High levels of phosphorus have been found in cancer cells, yet studies are lacking in the research literature that have examined a link between phosphate toxicity, breast cancer, and alcohol consumption. The present theoretical paper used a Grounded Theory Literature-Review Method to analyze published research findings and propose that the association of alcohol consumption with increased breast cancer incidence is mediated by alcohol-induced renal burden and nontraumatic rhabdomyolysis, leading to hyperphosphatemia and phosphate toxicity. Phosphate toxicity is also associated with increased cell-signaling in tumorigenesis, and phosphate toxicity is potentially a common factor linking cancer and kidney disease in onco-nephrology. Novel insights in this paper may lead to future research and interventions that raise public awareness of breast cancer risk and alcohol consumption, mediated by phosphate toxicity.

Chapter 4.

Study 2. “High dietary phosphorus is associated with increased breast cancer risk in a U.S. cohort of middle-aged women”

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Data Availability: https://www.swanstudy.org/swan-research/data-access/

4.1 Abstract

Research has shown that high amounts of dietary phosphorus that are twice the amount of the U.S. dietary reference intake of 700 mg for adults are associated with all-cause mortality, phosphate toxicity, and tumorigenesis. The present nested case–control study measured the relative risk of self-reported breast cancer associated with dietary phosphate intake over 10 annual visits in a cohort of middle-aged U.S. women from the Study of Women's Health Across the Nation. Analyzing data from food frequency questionnaires, the highest level of daily dietary phosphorus intake, >1800 mg of phosphorus, was approximately equivalent to the dietary phosphorus levels in menus promoted by the United States Department of Agriculture. After adjusting for participants' energy intake, this level of dietary phosphorus was associated with a 2.3-fold increased risk of breast cancer incidence compared to the reference dietary phosphorus level of 800 to 1000 mg, which is based on recommendations from the U.S. National Kidney Foundation, (RR: 2.30, 95% CI: 0.94–5.61, p = 0.07). Despite the lack of statistical significance, likely due to the small sample size of the cohort, the present nested case–control study's clinically significant effect size, dose–response, temporality, specificity, biological plausibility, consistency, coherence, and analogy with other research findings meet the criteria for inferred causality in observational studies, warranting further investigations. Furthermore, these findings suggest that a low-phosphate diet should be tested on patients with breast cancer.

4.2 Introduction

As global populations increasingly transition to the risk factor profile of Western nations, “dramatic changes in lifestyle” are affecting the prevalence of risk factors for breast cancer and other cancers (1). For example, a recent meta-analysis found that the highest dietary intake of a Western dietary pattern, including red or processed meats, high-fat dairy products, potatoes, and sweets, was associated with a 14% increased risk of breast cancer compared to the lowest intake (169). The same study found that the highest intake of a “prudent” dietary pattern, containing fruits and vegetables, fish, whole grains, and low-fat dairy, was associated with an 18% reduced risk of breast cancer compared to the lowest intake. Of relevance, the plant-based foods that predominate in a prudent dietary pattern tend to be lower in the essential mineral phosphorus than the animal-based foods typically found in a Western dietary pattern (170).

Inorganic phosphate (Pi) metabolism is regulated in the body by a sensitive network of endocrine hormones released by the kidney-bone-parathyroid-intestine axis (171). The accumulation of excess Pi in the tissues of the body due to dysregulated phosphate metabolism can produce a condition known as phosphate toxicity, and evidence supports the association of phosphate toxicity with tumorigenesis (20). For example, animal studies have shown that excessive dietary phosphate increases cell signaling in the promotion of cancer cell growth (34, 56). Notably, a “regulation-based model” of cancer research proposed by Schipper et al. in *The Lancet* in 1996 (149), suggests that cancer is a disease of dysregulated metabolism and may be reversable. The authors were referring to dysregulated metabolism in a general way relative to myriad metabolic processes in the human body, and not specifically to dysregulated phosphate metabolism. Based on the human genome, scientists predicted that 135 metabolic pathways are active in the body, most of which are related to nutritional metabolism (172). In general, metabolomics is currently contributing to the discovery of important metabolic alterations in the growth of cancer cells, with potential applications for clinical oncology (173).

Phosphorus in the form of dietary phosphate is plentiful in the dietary pattern eaten by contemporary western populations, including in Canada and the United States (174). Phosphate intake is also rising as people increase their consumption of foods processed with phosphate additives (175). Dietary sources contributing the greatest amount of phosphorus in the food Americans eat are milk and dairy products (cheese, ice cream, yogurt), bakery products (breads, rolls, tortillas), vegetables (starchy),

chicken, “Mexican dishes” (nachos, burritos, tacos), and pizza (176). Gastrointestinal bioavailability of phosphorus also varies in different dietary sources. For example, phosphorus in meat and dairy has a higher absorption rate (40-60%) compared to phosphorus bound to phytate in whole grains (20-50%), while phosphate additives widely used by the food industry in ultra-processed food have 90-100% bioavailability (177). Relatedly, recent systematic reviews and meta-analyses found an increased risk of breast cancer and other cancers associated with increased intake of ultra-processed food (178, 179). Another study found an increased risk of mortality from ovarian cancer and breast cancer associated with ultra-processed food intake (180).

As the intake of a nutrient like phosphorus rises above optimal levels for health, the increased concentration may eventually become toxic and even result in death (16). Although the U.S. dietary reference intake (DRI) for phosphorus is 700 mg/day in adult women and men (21), the 2015–2016 National Health and Nutrition Examination Survey (NHANES) reported that women, on average, consume 1189 mg and men consume 1596 mg of dietary phosphorus/day (181). By comparison, guidelines from the U.S. National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (K/DOQI) recommends that patients with progressive kidney disease restrict phosphorus intake to 800–1000 mg/day, depending on protein requirements (182). Indeed, higher dietary phosphorus intake starting at about 1400 mg per day has been associated with increased all-cause mortality in the U.S. population (183). Furthermore, based on *Dietary Guidelines for Americans, 2020-2025,* published by the United States Department of Agriculture (USDA), a MyPlate 2000-calorie daily menu that includes whole grains and fat-free milk provides approximately 1800 mg phosphorous (55), well above the 1400 mg of dietary phosphorus associated with increased mortality risk (183).

Three cups of fat-free milk, as recommended by USDA menu plans, supplies more than 700 mg of phosphorus, which is sufficient to meet adult requirements, but provides only about 13% of calories in a 2000-calorie diet (184); as a result, overall phosphorus intake would quite reasonably be expected to be even higher when other foods are included. Furthermore, a recent study funded by the U.S. National Cancer Institute found a 50% increased risk of breast cancer incidence associated with the highest milk intake compared to the lowest milk intake (185), possibly related to milk’s high phosphorus content. Three cups of milk a day was also associated with a 44% increased risk of cancer mortality compared to one cup (186). Also, a systematic review and meta-analysis found that dietary acid load is associated with a 58% increased relative risk of cancer (187), and dietary acid load and

phosphorus intake were lower in participants in a randomized controlled trial who consumed a vegan diet compared to a meat-rich diet (188).

The purpose of the present study is to investigate associations of breast cancer incidence with discrete categories of dietary phosphate levels. Phosphate levels are based on dietary guidelines from U.S. health organizations and government agencies, and categories also include levels of phosphate associated with disease in the research literature. The hypothesis in the present study is that the relative risk of breast cancer incidence is more strongly associated with high levels of dietary phosphate compared to low levels of phosphate. The rationale for selecting the National Kidney Foundation (NKF) guidelines for dietary phosphate intake as the reference level in this study is based on numerous findings implicating chronic kidney disease as a risk factor for cancer, such as Lees et al. (189), Wong et al. (159), Stengel (190), Tendulkar et al. (191), Kitchlu et al. (192), Hu et al. (161), Movahhed et al. (193), Wei et al. (194), Guo et al. (195), Na et al. (196), and Yu et al. (197). Additionally, high serum phosphate levels associated with tumorigenesis (20) are also prevalent in chronic kidney disease (198, 199). Conceivably, a low dietary level of phosphate that is least harmful in chronic kidney disease may also reduce risk of cancer. Therefore, the hypothesis of this observational study posits that the lowest level of phosphate intake, represented by the NKF recommendations (800 – 1000 mg), has a lower relative risk of breast cancer in the cohort compared to higher dietary phosphate levels.

4.3 Materials and Methods

The present study used a nested case-control design to conduct a secondary analysis of longitudinal cohort data from the Study of Women's Health Across the Nation (SWAN) (57). Case-control studies retrospectively measure the prevalence of an outcome within a group (200), for example, the odds that women in a group have breast cancer. However, because women in the SWAN cohort were free of breast cancer at enrollment, nesting the case-control study's longitudinal data within the SWAN cohort indicates the incidence of breast cancer. Incidence is measured with risks which are generally more accurate measurements than odds.

SWAN is funded by the U.S. National Institutes of Health, the National Institute on Aging, the National Institute of Nursing Research, the National Center for Complementary and Alternative Medicine, and the Office of Research on Women's Health, and the open access dataset for the SWAN study, along with demographic information of the cohort, is freely available online at the study

website (201). SWAN study participants include 3,302 multi-ethnic middle-aged American women from a multi-site longitudinal sample. “At the time of enrollment, women were premenopausal, not taking hormones and between 42–52 years of age. Figure 4 shows that participants identified themselves as African-American, Caucasian, Chinese, Hispanic, or Japanese (202).

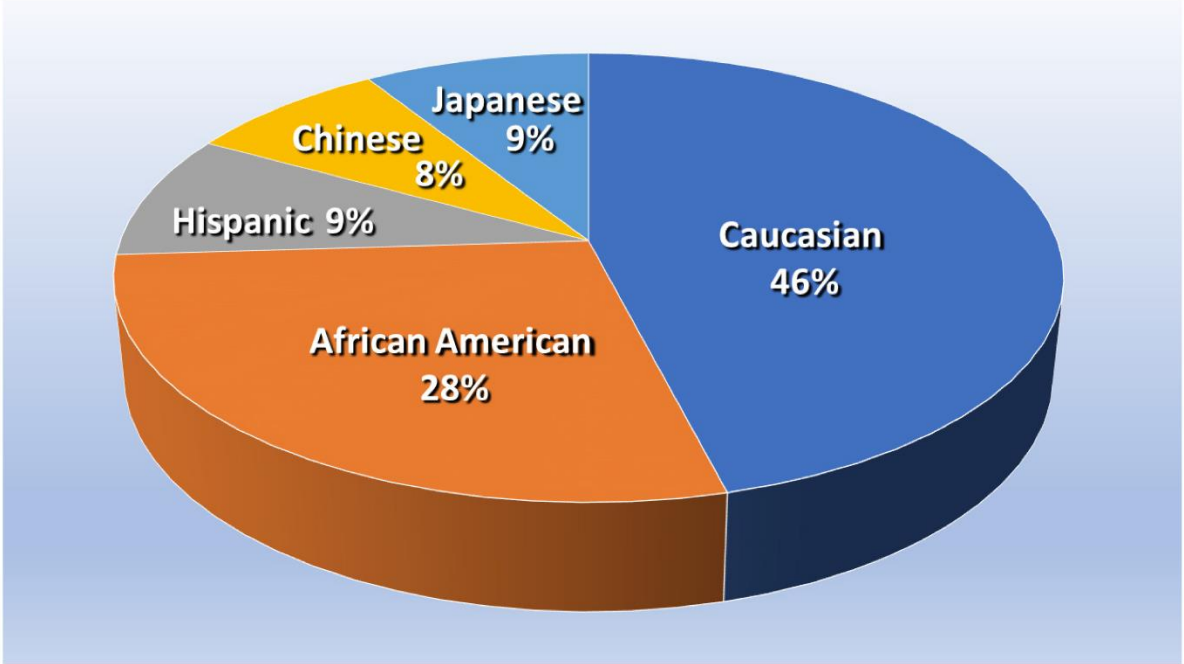

Figure 6. Proportion of SWAN participants, based on About SWAN—Study of Women’s Health Across the Nation (swan.org) (203).

Publicly available data from SWAN used in the present study was collected from baseline interviews and examinations of physical, psychological, biological, and social factors, followed up with 10 annual visits (1997-2007). Food frequency questionnaires (FFQs) were administered to collect dietary data at baseline and at visits 5 and 9. In the present study, each of 74 breast cancer cases, who self-reported breast cancer during annual follow up visits, were matched with four controls randomly selected from the cohort, totaling 296 controls consisting of women with similar ages (42-52 years) who were followed over 10 annual assessments. Four controls per case is recommended to increase statistical power in a case-control study, with beyond four matched controls generally leading to negligible increases in power (204). A list of random numbers was generated by Microsoft Excel to select controls.

4.3.1 Statistical Analysis

Although an odds ratio is most often used in case-control studies to measure the ratio of disease *prevalence* between exposed and unexposed groups, the present case-control study is nested within a cohort and measures disease *incidence* or an *incidence rate ratio* between exposed and unexposed groups, which is represented in the present paper as a risk ratio (205).

> "The numerator of an incidence proportion or rate consists only of persons whose illness began during the specified interval. The numerator for prevalence includes all persons ill from a specified cause during the specified interval regardless of when the illness began" (206).

Additionally, odds ratios in cohort studies overestimate the risk ratio (207). Relative risk formulas with 95% confidence intervals and p-values were calculated to four decimal places using online MedCalc Software Ltd (208). Statistical significance was set at $p<0.05$.

4.3.2 Dietary Assessment

Data of dietary phosphorus intake collected at baseline from food frequency questionnaires (FFQ) were cumulatively averaged with FFQ data collected in visits 5 and 9 according to the cumulative average method used by Wallace et al. (209). Specifically, the sum of phosphorus from three prior FFQ measures over 10 visits was divided by 3 to provide the final cumulative average. Willett stated, "The use of cumulative average measurements (i.e., the average of all measurements for an individual up to the start of each follow-up interval) takes advantage of all prior data and thus should provide a statistically more powerful test of association with cumulative exposure" (16). For example, a recent study on dietary flavonoids "used the cumulative average intake of flavonoids and other nutrients calculated by averaging their intake at baseline and each follow-up survey" (210). The same method to calculate cumulative average was used for calorie intake. Also, Wallace et al. handled missing FFQ data for visits 5 and 9 by imputing previously reported values, which is a single-imputation method known as last observation carry-forward (LOCF) (211). However, noting LOCF can have problems both with biased estimation and artificial reduction of variance (212), missing data in the present study were handled with procedures for multiple imputation calculated with SAS PROC MI using the Fully Conditional Specification Method (FCS).

Additionally, the adjustment method from the *Dietary Assessment Primer* of the National Cancer Institute (NCI) (213) was used in the present study to standardize self-reported dietary information by

adjusting for energy intake. According to the NCI, the purpose of energy adjustment is to mitigate "the effects of measurement error in data collected using self-reported dietary assessment instruments." Energy adjustment is based on "the assumption that individuals tend to misreport intakes of most reported foods and beverages to a similar degree and in the same direction" (e.g., less healthy foods are often underreported more than healthy foods). Information biases from underreported calorie and phosphorus intakes in FFQs were adjusted by estimating each participant's caloric density of phosphorus, calculated by dividing milligrams of phosphorus intake by caloric intake. This nutrient density quotient was then multiplied by 2000 calories needed for average bodyweight maintenance in women.

To analyze breast cancer risk ratios, energy-standardized dietary phosphorus intakes of participants were grouped into six discrete categories, each spanning 200 mg phosphorus (P), with 800 to 1000 mg P as the reference category to which the other five categories were compared. As mentioned in the introduction, the reference category is based on NKF guidelines for P dietary intake (182). The second phosphate category covers the range from >1000 to 1200 mg P. The third category ranges from >1200 mg to 1400 mg, which is the level associated with increasing all-cause mortality (183). The fourth and fifth categories range from >1400 mg to 1600 mg and >1600 to 1800, respectively, and the sixth category, >1800 mg P, is the approximate level of phosphate in menus recommended by the USDA. Supporting data for categorization of breast cancer cases and controls is available in Appendix A and Appendix B, respectively, and Appendix C and Appendix D contain data for the MI procedure for cases and controls, respectively. Table 2 shows the SWAN variables for Study 2.

Table 2. SWAN variables for Study 2.

Variable	**Description**
SWANID	Participant ID number
VISIT	Visit number
CANCERS	Cancer since last visit: 1 = no; 2 = yes
PSITECA	Primary site of cancer: 1 = one breast; 2 = both breasts
DTTPHOS	Dietary phosphorus mg, intake estimate
DTTKCAL	Dietary calorie intake estimate

4.4 Results

Table 3 shows the mean, standard deviation, minimum, and maximum values for P mg in the unadjusted and standardized case and control groups, rounded to multiples of 10. Mean unadjusted dietary P levels for the case and control groups are 1120 mg and 1150 mg, respectively, which are approximately equal to the average dietary P intake of 1189 mg reported for U.S. women in the 2015-2016 National Health and Nutrition Examination Survey (NHANES) (214). Group mean standardized P levels for the case and control groups increased to 1390 mg and 1320 mg, respectively, with an approximate 5% higher mean in the case group compared to the control group.

Table 3. P mg in case and control groups.

Group	Mean	SD	Min.	Max.
Cases, unadjusted (*N* = 74)	1120	330	360	1850
Cases, standardized	1390	340	770	2180
Controls, unadjusted (*N* = 296)	1150	380	330	2620
Controls, standardized	1320	290	570	2450

Interestingly, nine cases initially reported unadjusted dietary P levels below 800 mg (substantially below the NHANES average of 1189 mg P for U.S. women), which was reduced to two cases <800 mg P after standardization. Among controls, 62 women initially reported unadjusted dietary P levels below 800 mg which was reduced to eight controls after standardization. Standardization appeared to reduce the proportion of initially reported dietary P levels <800 mg more so in cases (2 out of 9 or 22.2%) than in controls (8 out of 62 or 12.9%). Table 3 also shows that the maximum standardized dietary P intake levels in the cases and controls are 2180 mg and 2450 mg, respectively, which are well below the 4000 mg tolerable upper intake limit (UL) for P to prevent harmful effects according to the Institute of Medicine (IOM) (21). The IOM notes that the UL was established to guide use of dietary supplements, and P is not often consumed in supplements in the U.S.

The standardized mean P intakes for cases and controls in our study (1390 and 1320 mg, respectively) are below P levels in My Plate recommendations (~1800). This suggests that My Plate recommendations may not be attainable for many people. Additionally, Table 3 shows that minimum levels of standardized dietary P in cases is 770 mg, which meets the daily recommended dietary allowance (RDA) of 700 mg for adult men and women according to the IOM. The IOM also noted

that RDAs provide additional P in women for lactation and pregnancy. By contrast, Table 3 shows that the standardized minimum level of dietary P is lower at 570 mg in the controls, yet this level is very close to the IOM's estimated average requirement (EAR) of 580 mg P for adult men and women.

Table 4 shows the division of standardized dietary P levels into six discrete dietary intake categories, each spanning 200 mg P. Estimated relative risks (RR) of breast cancer are calculated by comparing risks from each of five categories of P intake to the reference P intake level of 800-1000 mg (the control level). Risk and RRs in Table 4 are shown rounded to two decimal places, and 95% confidence intervals (CIs) cross the null value of 1, indicating statistical non-significance. However, an increasing risk of breast cancer is associated with exposure to higher P intake levels. Furthermore, the highest level of >1800 mg P is associated with the highest RR of breast cancer, 2.30, although the p-value is non-significant at 0.07.

Table 4. Relative risks of breast cancer cases associated with dietary P compared to reference.

Dietary P	Breast Cancer Cases	Controls	Risk	Estimated Relative Risk
800–1000 mg P	6	34	0.15	Reference
>1000–1200 mg P	13	58	0.18	1.22 (95% CI 0.50–2.96) p = 0.66
>1200–1400 mg P	20	93	0.18	1.18 (95% CI 0.51–2.72) p = 0.70
>1400–1600 mg P	14	62	0.18	1.23 (95% CI 0.51–2.95) p = 0.65
>1600–1800 mg P	9	22	0.29	1.94 (95% CI 0.77–4.86) p = 0.16
>1800 mg P	10	19	0.34	2.30 (95% CI 0.94–5.61) p = 0.07

A graph of the estimated risks of breast cancer incidence associated with P categories is shown in Figure 5.

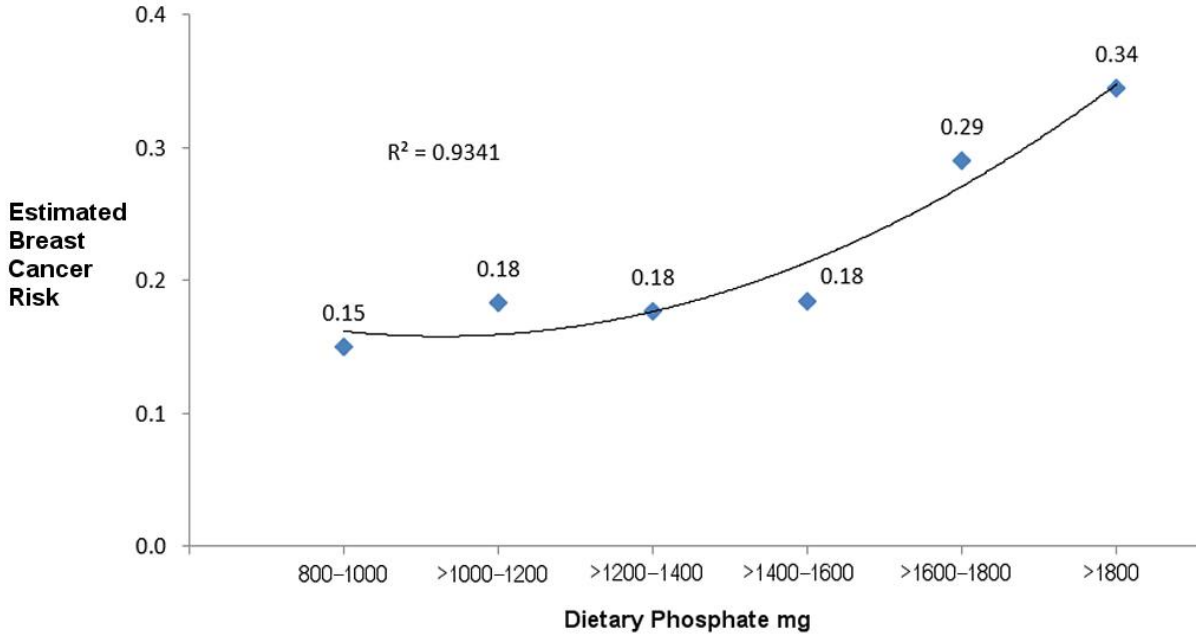

Figure 7. Risks of breast cancer incidence associated with categories of dietary P.

A curvilinear regression line fitted to the graph in Figure 5 has an R^2 of 0.9341, indicating a strong correlation between increasing dietary P levels and breast cancer risks.

4.5 Discussion

To the best of the authors' knowledge, the present study is the first to report an increased risk of self-reported breast cancer incidence associated with high dietary P intake. Risk is the rate of an event in a group, and risk in Study 2 is the rate of self-reported breast cancer in women grouped by categories of dietary P intake. Risk ratios divide the risk in each group by the risk of the reference group, which is the group in this study with the lowest dietary intake of 800–1000 mg P. Compared to the lowest P intake level in this nested case-control study from the SWAN cohort of middle-aged females, exposure to the highest P intake of >1800 mg is associated with a 2.30 relative risk of breast cancer incidence, although this effect is not statistically significant (95% CI 0.94–5.61, p = 0.07). Confidence intervals at 95% estimate the range of findings that have less than 5% probability of occurring by chance. A confidence interval of a risk ratio that includes the null value of 1 increases the statistical chance that both groups in the risk ratio have equal risks with no difference in group events, thereby rendering the risk ratio statistically nonsignificant. The p-value in Study 2 shows that the study effect is a modest 2% above the 5% value for statistical significance. The confidence

interval in Study 2 also shows that the effect size has a very high range of more than five and a half times the risk of the reference group in contrast with a much smaller 6% range below the reference group risk. Additionally, a curvilinear regression line of risks for breast cancer incidence in the present study shows a strong correlation with exposure to higher levels of dietary P; R^2 equals 0.9341.

Although the risk ratios in the study did not reach statistical significance, this may be due to the study's limited statistical power and small sample size—breast cancer cases were reported in only 2.2% of the cohort. Nevertheless, the practical significance of the study's large effect size is important, as "the effect size is the main finding of a quantitative study" (215).

Of particular concern is the 2.30 increased risk of breast cancer incidence associated with the highest level of >1800 mg P compared to the reference level of 800–1000 mg P. This high level of P is the approximate amount in menu plans promoted by the USDA. Powerful U.S. government agencies, the USDA and Health and Human Services, currently write the Dietary Guidelines for Americans, "separating the science from the actual guidelines and making the process more political" (216). Findings of the present study should alert the public to prioritize breast cancer prevention through promotion of dietary recommendations with lower P levels, which might also help reduce the global burden of 3 million new breast cancer cases predicted by 2040 (217).

Although RRs based on uncontrolled observational studies without randomization cannot prove causality, findings of the present study meet criteria proposed by Bradford-Hill which infer causality in observational studies (43).

1. Strength of association: The magnitude of the relative risk of breast cancer incidence associated with high dietary P levels is up to 2.3 times greater than associations with low phosphorus levels. "As a measure of effect size, an RR value is generally considered clinically significant if it is less than 0.50 or more than 2.00; that is, if the risk is at least halved, or more than doubled" (218). A recent review from the International Agency for Research on Cancer (IARC) found that most studies linking various cancers to occupational exposures known to be carcinogenic in humans reported relative risk values well below the 2.30 relative risk in the present study, and approximately one-third of the confidence intervals in the IARC review were not statistically significant (219).

2. Consistency: The association of high dietary P with breast cancer and other cancers is similar across studies (48, 53, 220).
3. Specificity: The present study shows that P is a specific dietary factor in the association with breast cancer; notably, this does not preclude other risk factors that are associated with breast cancer.
4. Temporality: Exposure to high dietary P precedes breast cancer incidence, as revealed in the present nested case-control study's longitudinal data.
5. Biological gradient: Compared to the lowest level of P intake, increasing levels of dietary P in the present study are associated with increasing risk of breast cancer.
6. Plausibility: Higher dietary P levels are associated with dysregulated phosphate metabolism and phosphate toxicity, which may lead to tumorigenesis (20, 221-224).
7. Coherence: Dysregulated phosphate metabolism and phosphate toxicity fit the regulation-based model of cancer which proposes that cancer is caused by dysregulated metabolic factors (149).
8. Experimental evidence: Laboratory animal experiments confirm an association between high dietary P feeding and tumorigenesis (34, 56). Importantly, P from dietary sources in these animal experiments are not administered at the maximum tolerated dosages for chemical agents, which are often used in carcinogenic studies (225).
9. Analogy: Overgrowth of algae blooms in eutrophication, caused by excessive phosphate fertilizer agricultural runoff (226), is analogous to the ecosystem dynamics of cancer cell overgrowth (227) associated with high dietary P in the Western diet (169, 174).

The study's main strength is that it is the first report to show a large positive dose-dependent association between self-reported breast cancer incidence and increasing levels of dietary P intake in a cohort of middle-aged U.S. women. Limitations of the study include the small sample size of 3,302 women in the SWAN cohort compared to nationwide studies of over 161,000 women in the Women's Health Initiative (228) and 280,000 women in the Nurses' Health Study (229). However, the SWAN cohort provides the advantage of a broad ethnic cross-section of middle-aged women in the national population. Furthermore, Pink SWAN, supported by the National Cancer Institute, doubled the follow-up period of the SWAN cohort from 10 to 20 years, and Avis et al. identified 152 breast cancer cases (230), which is approximately twice the sample size of the present study.

Additionally, the nested case-control design of this study has certain limitations common to observational studies:

"The major disadvantage of nested case-control studies is that not all pertinent risk factors are likely to have been recorded. Furthermore, because many different healthcare professionals will be involved in patient care, risk factors and outcome(s) will probably not have been measured with the same accuracy and consistency throughout. It may also be problematic if the diagnosis of the disease or outcome changes with time" (231).

Nevertheless, among epidemiological observational studies, the nested case-control design ranks high, providing the advantage of observing disease incidence within a cohort (232).

Other study limitations include the reliance on cohort participants to self-report breast cancer incidence, which may be prone to inaccuracies and information bias, unless credible proof of diagnosis is presented to verify the diagnosis. Study limitations also include standardization of self-reported dietary intake from FFQ data. Although standardization is intended to provide a more realistic estimation of dietary intake to improve validity of the study, standardization cannot estimate actual dietary intake levels, and adjustments are based on averages rather than individual caloric needs of women. More accurate dietary information can be obtained using intervention studies with controlled feeding of participants—which can be very expensive. Furthermore, researchers have found a correlation between dietary phosphate intake and phosphate excreted in 24-hour urine collection, which has potential use as a biomarker to estimate dietary phosphate intake in clinical studies (233). However, compared to short-term measures such as 24-hour recall, FFQs are the most often used dietary tool for epidemiological studies with long follow-up periods (234).

Finally, potential confounding factors were not controlled in this observational study, such as exposures to environmental carcinogens, including alcohol and tobacco, and other risk factors like obesity, low physical activity, and family history of breast cancer (235). Phosphorus needs may also decline during menopause compared to the reproductive years—which could explain findings of a study in which women at post menopause had increasing levels of serum P (236), which could also be related to increasing breast cancer risk as women age (237). For example, although reproductive function wanes in menopause and the demand for phosphorus decreases, if dietary phosphorus intake remains high due to accustomed eating habits developed when younger, a woman in menopause may be at risk for elevated serum phosphate from the uneliminated

dietary phosphate excess. Additionally, a participant's individual renal function may modify the regulatory effect of dietary phosphate on breast cancer. Future studies should control for effect modification by stratifying the results according to participants' estimated glomerular filtration rate or other biomarkers of renal function. Furthermore, renal function declines with age (238), and so findings of dietary phosphate and breast cancer in this middle-aged female SWAN cohort cannot be generalized to other segments of the population.

Ultimately, the most thorough and appropriate method to test for known and unknown confounding factors in the association of phosphate toxicity with tumorigenesis is through randomized controlled trials, as recommended by the National Cancer Institute (76). Importantly, findings from the present study corroborate other evidence indicating the strong specificity of phosphorus as an essential nutrient independently associated with tumorigenesis, which was emphasized in a recent review by Arnst and Beck Jr. ((48)). Other vitamins, minerals, and nutrients including carbohydrates, fats, and proteins, have also been associated with cancer, but according to the National Cancer Institute no nutrient has yet been established in the research literature as a causative carcinogenic factor (76). Furthermore, failure to link a specific nutrient with cancer after many decades of research has led to this research approach falling out of favor, and current approaches now focus on dietary patterns (239). However, multifactorial studies of dietary patterns are beyond the scope of the present thesis. Additionally, the independent association of phosphate with tumorigenesis is in accordance with the principle of parsimony which proposes that the simplest explanation with the fewest entities is the best explanation of an observed phenomenon ((240).

For future research on cancer therapies, Kuang et al. wrote, "our simulation results show that if an artificial mechanism (treatment) can cut the phosphorus uptake of tumor cells in half, then it may lead to a three-quarter reduction in ultimate tumor size, indicating an excellent potential of such a treatment" (222). Furthermore, according to the National Institute of Cancer of the U.S. National Institutes of Health, "When evidence emerges from an epidemiologic study that a dietary component is associated with a reduced risk of cancer, a randomized trial may be done to test this possibility" (76). Based on the epidemiologic evidence in the present study finding a clinically significant reduced

risk of breast cancer incidence associated with low levels of dietary P compared to higher levels, further clinical studies are warranted to test a low-phosphate diet on tumor reduction in breast cancer patients.

4.6 Conclusions

Risk factors for breast cancer include the Western diet, which is high in the essential mineral P. Research has shown that higher amounts of dietary P are associated with disease and mortality. The present nested case-control study measured risk ratios of dietary P levels associated with self-reported breast cancer in middle-aged women from the SWAN cohort. Results in ten annual follow-up visits found that the highest dietary intake of P was associated with a clinically significant 2.30 relative risk of breast cancer incidence compared to the lowest intake level recommended by the U.S. NKF to treat chronic kidney disease. The highest level of P intake is within the approximate range promoted by the USDA. Evidence supports criteria to infer breast cancer causation from high dietary P intake, and further studies with larger cohorts are warranted. Additionally, clinical and preclinical studies with breast cancer patients should test the effect of a low-phosphate diet already in use for patients with chronic kidney disease.

Chapter 5.

Study 3. "Breast cancer and bone mineral density in a U.S. cohort of middle-aged women: Associations with phosphate toxicity"

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Data Availability: https://www.swanstudy.org/swan-research/data-access/

5.1 Abstract

Breast cancer is associated with phosphate toxicity, the toxic effect from dysregulated phosphate metabolism that can stimulate tumorigenesis. Phosphate toxicity and dysregulated phosphate metabolism are also associated with bone mineral abnormalities, including excessive bone mineral loss and deposition. Based on shared associations with dysregulated phosphate metabolism and phosphate toxicity, a hypothesis proposed in the present mixed methods–grounded theory study posits that middle-aged women with incidence of breast cancer have a greater magnitude of changes in bone mineral density over time compared with women who remained cancer-free. To test this hypothesis, a mixed-effects model was used to analyze the associations of breast cancer incidence with spinal bone mineral density changes in the U.S. Study of Women's Health Across the Nation. Compared with women in the cohort who remained cancer-free, women who self-reported breast cancer had higher bone mineral density at baseline but had more rapid losses in bone mineral density during follow-up visits. These findings agree with the hypothesis that a greater magnitude of changes in bone mineral density over time is associated with breast cancer in a cohort of middle-aged women. The findings also have implications for studies investigating dysregulated phosphate metabolism and phosphate toxicity as causative factors of bone metastasis in metastatic breast cancer. Additionally, the authors previously found increased breast cancer risk associated with high dietary phosphate intake in the same cohort of middle-aged women, and more studies should investigate a low-phosphorus diet to reduce bone mineral abnormalities and tumorigenesis in breast cancer patients.

5.2 Introduction

An association of breast cancer with high bone mineral density (BMD) has been reported in the research literature (241), but the underlying causative mechanisms of this relationship have not been established. For example, a 2013 meta-analysis of ten prospective studies involving 70,878 postmenopausal women found that high BMD was associated with increased breast cancer risk (242). Also in 2013, a retrospective study of Israeli women found an association between breast cancer and higher BMD in the lumbar spine, femoral neck, and total hip (243). A more recent case-control study in 2019 confirmed that breast cancer in Brazilian women is associated with high BMD in the lumbar spine, but not in the femoral neck or total femur (244). Interestingly, a 2022 case-control study reported that BMD in women with breast cancer was higher compared to a control group, even though breast cancer cases had lower average vitamin D levels which are normally associated with bone health (241).

Further contributing to the research literature on bone mineral density and breast cancer is the opposite finding of increased osteoporosis risk associated with breast cancer in postmenopausal women, suggesting that breast cancer may share common "biochemical links" with low bone mineral density (245). However, treatment for breast cancer is also associated with bone loss (246), and treatment effects must be considered in assessing osteoporosis risk associated with breast cancer in women. On the other hand, hormone replacement therapy (HRT) increases BMD, and HRT is also associated with increased risk for breast cancer (247). These findings suggest that both high and low BMD may be biochemically linked to breast cancer through unknown factors.

Adding to the controversy, other studies have failed to find an association between breast cancer and BMD (29, 248-250). Part of this inconsistency in study findings may be explained by differing intervals of repeated follow-up measures to detect longitudinal changes in bone mineral density related to the incidence of breast cancer (29). Importantly, healthy bone mineral density levels are neither excessively high, nor low, and elevated bone mass has been associated with degenerative bone disease such as osteoarthritis (251, 252).

Coincidently, phosphate toxicity, the pathogenic effect of dysregulated phosphate metabolism in the body, is not only associated with tumorigenesis (20, 48-53) but also negatively impacts bone health (253), implying that phosphate toxicity could be a potential factor that mediates the association of breast cancer with abnormal bone mineral density . Yet, no studies have investigated phosphate

toxicity and dysregulated phosphate metabolism as a factor associated with high and low levels of bone mineral density in breast cancer. A brief description of phosphate metabolism and phosphate toxicity follows.

Metabolism of serum inorganic phosphate (Pi) is regulated through endocrine hormones secreted by a bone-kidney-intestine-parathyroid axis (25). Intestinal absorption of Pi is increased as the kidneys release the bioactive form of vitamin D, $1,25(OH)_2D_3$, also known as calcitriol. The kidneys reabsorb Pi to maintain normal serum Pi levels and excrete excess Pi in the urine. Fibroblast growth factor 23 (FGF23) released from bone, and parathyroid hormone (PTH) released from the parathyroid glands, help regulate Pi levels by inhibiting kidney reabsorption of excessive Pi and increasing urinary phosphate excretion.

Phosphate toxicity from excessive accumulation of phosphate in the tissues of the body can accelerate aging, cause bone deformities, and reduce longevity (254). Importantly, hyperphosphatemia (excessive amounts of Pi in the serum) can lower serum calcium levels, triggering PTH to resorb bone and release calcium into the serum to restore normal levels of calcium. Dysregulated amounts of serum Pi also raise calcium-phosphate levels, increasing ectopic calcification throughout the body, including calcium-phosphate deposits of hydroxyapatite in soft tissue and bone (25). Moreover, high calcium-phosphate product is associated with C-reactive protein (255), and C-reactive protein is associated with bone mineral loss (256).

Using a mixed-methods approach to analyze both quantitative and qualitative data (257), the present study investigated longitudinal changes in bone mineral density associated with breast cancer incidence in the U.S. Study of Women's Health Across the Nation (SWAN) (258). The authors previously found a 2.3 relative risk of breast cancer in the SWAN cohort associated with high daily dietary phosphate intake of >1800 mg compared to 800–1000 mg (RR: 2.30, 95% CI: 0.94–5.61, $p = 0.07$) (259). The present study uses a mixed methods-grounded theory design (MM-GT) to combine qualitative and quantitative data in theory development (36). The study follows a MM-GT design similar to the three phases described by Shim et al. (260): a qualitative exploratory and theory development phase, a quantitative confirmatory phase, and a final integration phase. In the present study, the research literature was rigorously and objectively reviewed using a grounded theory literature-review method, as described by Wolfswinkel et. al (37), and a hypothesis was generated for

quantitative testing using a mixed-effects model (Figure 6). Results of the quantitative analysis were then integrated with the qualitative evidence in the final discussion of the paper.

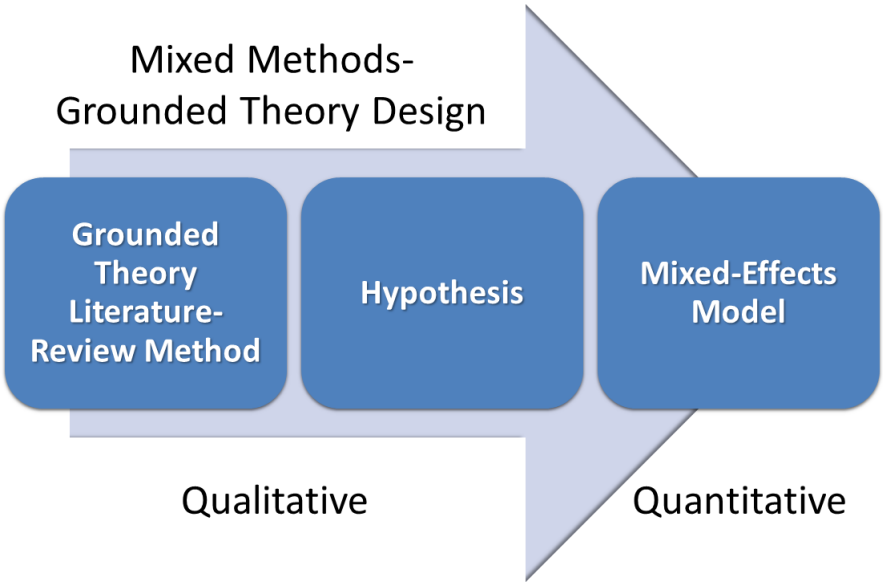

Figure 8. Mixed methods–grounded theory design.

5.3 Qualitative Analysis – Grounded Theory Literature Review

In the qualitative analysis of the present MM-GT study, research findings on phosphate toxicity, breast cancer, and bone mineral density were selected from all relevant sources for comparative analysis of concepts consisting of pathophysiological relationships and mechanisms. Concepts are the building blocks of qualitative analysis in the present MM-GT study.

> **"**Concept formation in qualitative research is a systematic process whereby the researcher sets definitions for important concepts that emerge during the research. These definitions help to provide the parameters for the qualitative study" (261).

"Sensitizing concepts" that guided development of the MM-GT study included basic phenomena important to the study, such as dysregulated phosphate metabolism, bone mineral density, and tumorigenesis. A narrative text cited research findings about these concepts, and a discussion synthesized these findings into pathophysiological relationships and mechanisms until a novel qualitative theory emerged. The theory explains the metabolic mechanisms by which phosphate toxicity and dysregulated phosphate metabolism are potentially associated

with changes in bone mineral density and tumorigenesis (262). More information on grounded theory is provided in Chapter 1.3. Note also that the sensitizing concepts are the starting point for the theory, and that other concepts may be introduced as the theory develops.

5.3.1 Phosphate Toxicity and Tumorigenesis

The following includes a brief summary of findings cited in a review of phosphate toxicity and tumorigenesis (20). Elevated levels of Pi within the tumor microenvironment stimulate cell signaling in tumorigenesis (32) and stimulate tumor neovascularization in lung and breast cancer cells (146). In a 1955 article, Ward and Griffen described findings from previous research in which excess phosphate uptake into nuclear RNA of cells was shown to stimulate tumor growth in precancerous rats, which was delayed when phosphorus uptake was suppressed (27). Sodium-phosphate cotransporters that sequester extracellular Pi are overexpressed in cancer cells of the ovaries (263), and a conference abstract published in 2014 in the *Annals of Oncology* (2022 Impact Factor: 50.5) reported overexpression of sodium-phosphate cotransporters in cancer cells of the lung, breast, and thyroid gland (264). The rate of transport of high Pi concentrations into breast cancer cells through H+-dependent Pi transporters is five-times that of sodium-phosphate cotransporters (51). Additionally, a letter published in *Science* as far back as 1946 noted detection of breast tumors through increased uptake of the radioactive isotope phosphorus-32, compared to lower uptake of the phosphorus isotope by normal breast tissue (265). In a recent perspective article by the author of the present thesis, effects of cancer cachexia in a mouse model that overexpress the tumor-suppressing P53 gene were compared with a mouse model of phosphate toxicity in ageing. The author demonstrated that effects of cancer cachexia in the overexpressed P53 phenotype were similar to effects of phosphate toxicity, with sarcopenia (muscle-wasting), osteoporosis, spinal kyphosis, organ atrophy, and reduced longevity (224).

Hyperphosphatemia in patients is associated with chromosome instability and increased proliferation of parathyroid cells (147), and elevated levels of Pi in extracellular tissue is associated with cancer metastasis in a mouse model of breast cancer (148). High dietary intake of phosphate in the Health Professionals Follow-Up Study was associated with high-grade prostate cancer (266), and another study found that serum phosphate levels were abnormally higher in cancer patients compared to control patients (129). Experimental animals fed high-phosphorus diets developed lung tumors (34)

and skin cancer (56). Furthermore, tumor cells of the lung and colon in humans contain up to twice the amount of Pi as normal cells (267).

5.3.2 Bone Remodeling and Dysregulated Phosphate Metabolism

Normal bone metabolism renews bone tissue through a balance of mechanisms that break down and remove worn bone tissue, and replace discarded tissue with deposits of new bone:

> "Bone remodeling is the process by which bone is renewed to maintain bone strength and mineral homeostasis. Remodeling involves continuous removal of discrete packets of old bone, replacement of these packets with newly synthesized proteinaceous matrix, and subsequent mineralization of the matrix to form new bone. The remodeling process resorbs old bone and forms new bone to prevent accumulation of bone microdamage"(268).

If bone remodeling mechanisms that normally build up and break down bone become unbalanced, metabolic bone disorders may occur, such as osteoporosis in which "bone resorption outpaces bone formation" (269). Of relevance, mineral and bone disorder is associated with chronic kidney disease (CKD-MBD), in which serum Pi homeostasis is often dysregulated (58, 59). Additionally, "studies have shown that patients with chronic renal failure (CRF) are more likely to suffer from breast cancer and other malignant tumors" (270). Furthermore, dysregulated phosphate and phosphate toxicity potentially mediates an association of mineral bone disorder with breast cancer by causing excessive release of PTH in hyperparathyroidism (known as secondary hyperparathyroidism).

> "PTH can produce catabolic or anabolic effect(s) on bone metabolism depending on the level of the hormone, periodicity, and duration of exposure" (271).

Loss of healthy bone in cancer is found in combination with increases in abnormal bone deposits, or osteoblastic skeletal lesions (60, 272). Abnormal calcification of bone is seen in metastasis of the breast, prostate, and other cancers (273). Bone deposits are also associated with osteosclerosis, a hardening in which excess minerals are abnormally deposited into the bone matrix (274). Main causes of osteosclerosis include secondary hyperparathyroidism (275), which is commonly associated with hyperphosphatemia in renal insufficiency (276). "It has already been established that in end-stage renal disease, hyperphosphatemia causes soft tissue calcification," and dysregulated phosphate metabolism may be responsible for observed associations of calcification in normal populations

(277). Additionally, ectopic calcification from calcium-phosphate deposits in the form of microcalcifications of the breast have been associated with increased risk of breast cancer (278).

Low vitamin D levels associated with dysregulated phosphate metabolism are common in CKD (279), and breast cancer risk is inversely associated with levels of vitamin D (167). Breast cancer metastasis is also autonomously promoted by vitamin D deficiency (280). Furthermore, evidence suggests that increased breast cancer risk is associated with high levels of FGF23 (281) and PTH (30), which are also associated with dysregulated phosphate metabolism.

5.3.3 Metastatic Breast Cancer

Metastatic breast cancer, stage IV breast cancer that has spread to other organs, is the most advanced form of breast cancer affecting approximately 30% of women with the disease, and is “generally incurable” (282). Bone is the most common site of metastases in metastatic breast cancer (283). Importantly, both abnormal bone deposition and bone loss (osteolytic skeletal lesions) appear early in metastatic breast cancer, but breast cancer metastases mostly cause bone loss:

> “Metastases leading to overall bone loss are classified as osteolytic. Those leading to excess bone deposition are considered osteoblastic. However, both bone degradation and deposition likely occur early in the metastatic process. The majority of breast cancer metastases ultimately cause bone loss (273).”

Although breast cancer bone metastases are predominantly osteolytic, 15–20% of breast cancer bone metastases cases “have a predominant osteoblastic component” (284). Excessive bone deposition in early osteoblastic metastases may account for the increased risk of breast cancer associated with higher BMD. Furthermore, Ramirez and Fielder noted that a "high local phosphate concentration during osteolysis" is observed in breast cancer and bone metastases, which requires further investigation (285). These findings provide plausible mechanisms by which dysregulated phosphate metabolism and phosphate toxicity are associated with BMD changes in breast cancer.

5.3.4 Hypothesis

A synthesis of concepts from the previously reviewed literature explains how abnormal bone mineralization and tumorigenesis share associations with dysregulated phosphate metabolism and phosphate toxicity. The rationale used to inform the hypothesis of the present study is based on transitive inference —"the process of inferring the relation between two items based on their shared

relation with a third item"(286). For example, Figure 7 proposes that abnormalities in BMD are transitively associated with breast cancer (dashed arrow) through shared associations with dysregulated phosphate metabolism and phosphate toxicity. Therefore, based on shared associations with phosphate toxicity, the study hypothesis is that women in the SWAN cohort who self-reported breast cancer incidence during follow up visits have a greater magnitude of changes in bone mineral density over time compared to women who remained cancer-free.

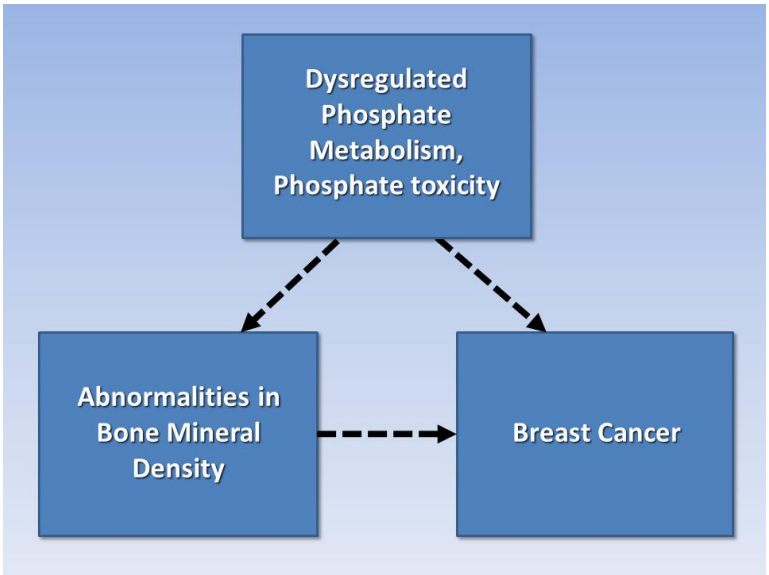

Figure 9. Abnormalities in bone mineral density in breast cancer.

Transitive associations with breast cancer through shared associations (dashed arrows) with dysregulated phosphate metabolism and phosphate toxicity.

Quantitative Analysis – Mixed-Effects Model

Quantitative analysis in the present MM-GT study uses frequent repeated measures to investigate the association of self-reported breast cancer with longitudinal changes in bone mineral density, based on a secondary analysis of follow-up data from the SWAN study (258). The SWAN dataset is a multi-ethnic, multi-site longitudinal sample of middle-aged American women, consisting of baseline interviews and examinations of biological, physical, psychological and social factors, with ten annual follow-up visits (201). SWAN is co-sponsored by the National Institute of Nursing Research, the National Institute on Aging, the National Institutes of Health-Office of Research on Women's Health,

and the National Center for Complementary and Alternative Medicine. The SWAN dataset and demographic information is freely available to the public online (See Data Availability Statement).

Between 1996–1997, 3302 women aged 42–53 years who were free of breast cancer were enrolled in the SWAN cohort (202). Participants identified themselves as African American (28%), Caucasian (46%), Chinese (8%), Hispanic (9%), or Japanese (9%). In annual follow-up interviews, participants were asked to self-report any diagnoses or treatments for breast cancer they had received since their last visit. Within the cohort, 2335 women were also enrolled at baseline to receive dual energy X-ray absorptiometry (DEXA) bone mineral scans of the lumbar spine and femoral neck during follow-up visits (287). Values in the dataset for bone mineral scans are in grams/cm^2 for absolute bone mineral density with cross-calibration applied at each visit number.

The present study examined longitudinal data from the SWAN cohort totaling 151 self-reports of cancer incidence in at least one breast, and over 17000 DEXA scans of the lumbar spine BMD values of the lumbar spine in grams/cm^2 are listed in the data set as variable SPBMDT. SWAN variables for Study 3 are listed in Table 5.

Table 5. SWAN variables for Study 3.

Variable	Description
SWANID	Participant ID number
VISIT	Visit number
CANCERS	Cancer since last visit: 1 = no; 2 = yes
PSITECA	Primary site of cancer: 1 = one breast; 2 = both breasts
SPBMDT	Spine bone mineral density, g/cm^2

Analysis was performed by fitting a linear mixed-effects regression model to the data using the PROC MIXED statistical analysis procedure in SAS, release 9.04.01M3P06242015. Fixed effects in a mixed-effects model are the constant or fixed relationships assumed between independent and dependent variables, so that "only the dependent variable changes in response to the levels of independent variables" (288). Fixed effects in the model of the present study quantify the association between spinal BMD in grams/cm^2 (the response variable, SPBMDT) in women self-reporting breast cancer incidence vs. women remaining cancer-free (the main independent variable of interest). In addition to fixed-effect responses in groups, the model's random effects include analysis of BMD

values from individual participants, which adds more detailed response information to the model. Importantly, random effects are specifically related to some unknown or latent variable in individuals, and "by including random-effects in the model, it is possible for researchers to account for multiple sources of variation" (289).

The general formula for the linear regression mixed-effects model used in the present study is based on Hedeker and Gibbons (290):

$$y_{ij} = \beta_0 + \beta_1 t_{ij} + \beta_2 x_j + \beta_3 (t_{ij} * x_j) + \upsilon_{1i} t_{ij} + \varepsilon_{ij} \quad (1)$$

where y_{ij} denotes the i^{th} individual's continuous BMD values (the dependent variable) at the j^{th} repeated measurement.

β_0 is the y-intercept between individuals.

$\beta_1 t_{ij}$ is the time or trend effect between individuals denoted by the j^{th} individual annual visit = 0, 1, 2, 3, 4, 5, 6, 7, 8, 9.

$\beta_2 x_j$ is the i^{th} individual's self-reported breast cancer status (the independent variable) = 1 if yes for breast cancer, 0 otherwise.

$\beta_3 (t_{ij} * x_j)$ is the interaction of $\beta_1 t_{ij}$ and $\beta_2 x_j$, the effect of time on the independent variable.

υ_{0i} is the random y-intercept within individuals.

$\upsilon_{1i} t_{ij}$ is the random trend effect within individuals.

ε_{ij} *is* the residual error within individuals.

5.3.5 Quantitative Model Selection

The principle of parsimony in statistics "states that a model should be as simple as possible," whereas overfitting a model with too many parameters "risks identifying spurious factors as important" (291). The model that best fit the SWAN data in the present study was selected using Akaike Information Criterion (AIC) (292). The best-fitting model often has the lowest AIC score, which explains the greatest amount of variation, based on maximum likelihood estimates, and has the fewest independent variables. Maximum likelihood estimation fits a distribution curve to data so that the likelihood that data falls under the distribution curve is maximized (293). During model selection, a mixed-effects model is scored and compared in a stepwise recursive procedure, adding variables from the general

formula of the model one at a time. Moreover, statistical significance of the variables is another important factor to consider in model selection, and interactive variables, the product of two or more independent variables (294), are also fitted. The specific interactive variable in the present study, the product between time and self-reported breast cancer status, was added to investigate if there are different trajectories of the BMD response over time for women who self-reported breast cancer versus women who did not.

Missing data handled by the present study's mixed-effects model are assumed missing at random (MAR), which means that the factors represented by the missing data are unlikely to have contributed to the cause of the data's absence (295). Furthermore, maximum likelihood in mixed-effects models has the advantage of forming unbiased estimates with minimal standard error that can consider the uncertainty of missing data, without the need for data imputation (296).

5.4 Results

The hypothesis in the present MM-GT study was tested by analyzing longitudinal data from the SWAN cohort of middle-aged women. A mixed-effects linear regression model was used to examine bone spinal mineral density changes in women who self-reported breast cancer compared to women who remained cancer free. A stepwise recursive procedure was used to fit the mixed-effects model to the SWAN data (Appendix E). Table 6 shows that fit statistics of the final selected model include the AIC and AICC (corrected for smaller samples) of -60138.1, and the BIC (Bayesian Information Criterion) of -60089.8.

Table 6. Fit statistics.

-2 Log Likelihood	-60154.1
AIC (Smaller is Better)	-60138.1
AICC (Smaller is Better)	-60138.1
BIC (Smaller is Better)	-60089.8

The notated formula for the final selected mixed-effects model is:

$$y_{ij} = \beta_0 + \beta_1 indiv\_visit_{ij} + \beta_2 brstcan_i + \beta_3 (indiv\_visit_{ij} * brstcan_i) + \upsilon_{0i} + \upsilon_{1i} indiv\_visit_{ij} + \varepsilon_{ij} \quad (2)$$

Table 7 lists estimates for the final selected model's y-intercept, self-reported breast cancer (BRSTCAN), individual visit number (INDIV_VISIT), and the interaction of breast cancer with

individual visit (INDIV_VISIT*BRSTCAN). All estimates are statistically significant at p<.05. Of note, the stepwise recursive procedure (Appendix E) shows that the p-value of BRSTCAN reduced from 0.8098 to 0.0042 when the interaction of breast cancer with individual visit was added to the final model, indicating a statistically significant longitudinal effect of breast cancer incidence over ten visits.

Table 7. Model estimates.

Effect	Breast Cancer	Estimate	Std Error	DF	t Value	Pr > |t|
Intercept		1.0837	0.003106	2212	348.88	<.0001
INDIV_VISIT		-0.00937	0.000201	2121	-46.58	<.0001
BRSTCAN	Yes	0.02130	0.007439	13E3	2.86	0.0042
BRSTCAN	No [Ref]	0	.	.	.	.
INDIV_VISIT*BRSTCAN	Yes	-0.00411	0.001302	13E3	-3.15	0.0016
INDIV_VISIT*BRSTCAN	No [Ref]	0	.	.	.	.

The final selected mixed-effects model with estimated coefficients from Table 7 is:

$$\hat{y}_{ij} = 1.0837 - 0.00937 indiv\_visit_{ij} + 0.02130 brstcan_i - 0.00411(indiv\_visit_{ij} * brstcan_i) \quad (3)$$

The panel below (Figure 8) contains BMD values of randomly selected women who were analyzed with the linear mixed-effects model; three women in the upper row who remained cancer-free, and three women in the lower row who reported breast cancer. The panel shows that the model fit the regression lines to data exceedingly well, even when data diverged from the population average, implying a small residual variance, ε in the general formula for the linear mixed-effects model.

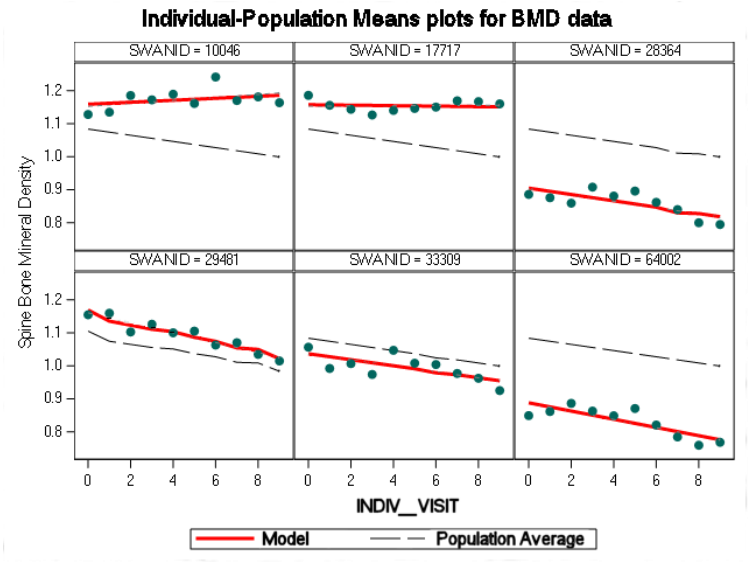

Figure 10. Panel of regression line fit to data.

(Green dots represent BMD per visit).

The mixed-effects model's estimates of spinal bone mineral density values for women in the SWAN cohort throughout 10 individual visits are shown as g/cm^2 in Table 8. Note that labelling the first visit as 0 begins the model's estimated BMD of women free from breast cancer at 1.0837 g/cm^2, the value of the y-intercept. Differences in BMD between the groups show that BMD in the breast-cancer group is 0.0213 g/cm^2 higher than the other women at the first visit. The rate of BMD decline per visit for each group (visit 2 minus visit 1) is 0.01348 g/cm^2 in the breast-cancer group, which is 0.00411 g/cm^2 greater than the rate of BMD decline per visit of 0.00937 g/cm^2 in the cancer-free women. And yet, even with a higher rate of decline in the breast-cancer group, the mean BMD in both groups averaged over ten years was almost identical. Spinal bone mineral density values are graphed as linear regression lines in Figure 9.

Table 8. Model estimates of spinal BMD, g/cm^2.

Visit	Breast Cancer Yes	Breast Cancer No	Difference
1	1.105	1.0837	0.0213
2	1.09152	1.07433	0.01719
3	1.07804	1.06496	0.01308
4	1.06456	1.05559	0.00897

5	1.05108	1.04622	0.00486
6	1.0376	1.03685	0.00075
7	1.02412	1.02748	-0.00336
8	1.01064	1.01811	-0.007046
9	0.99716	1.00874	-0.01158
10	0.98368	0.99937	-0.01569
Mean	1.04434	1.04154	0.0028

The graph of regression lines in Figure 9 shows longitudinal changes in BMD values of women who self-reported incident breast cancer during annual visits compared to women who remained free of breast cancer. The fixed effect of the model shows that, on average, values for spinal BMD declined over time for all women in the cohort. However, women who reported breast cancer had higher BMD at baseline, which decreased throughout the follow-up periods at a faster rate (steeper declining slope) than women without breast cancer. By the end of the study, women who reported breast cancer had crossed over to lower levels of BMD compared to women without breast cancer.

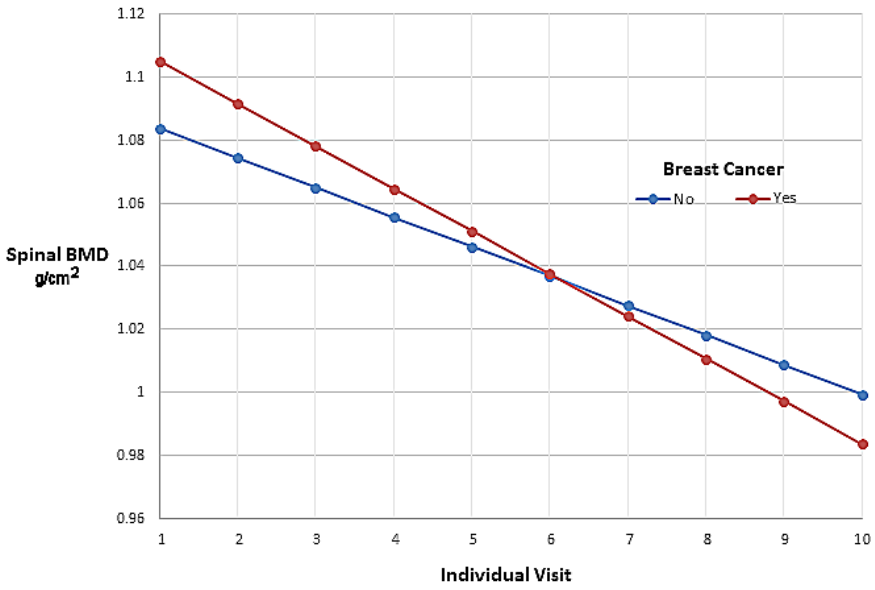

Figure 11. Mixed-effects model regression estimates.

5.5 Discussion

The fixed effect of the mixed-effect model in the present study shows that, on average, all women of the SWAN cohort lost BMD over ten annual visits. However, random effects of the model show that women who reported breast cancer during follow-up visits had higher BMD at baseline than women who remained free of breast cancer. This is consistent with other research findings associating high BMD with risk of breast cancer (241-244). Furthermore, women who reported breast cancer lost BMD at a faster rate throughout the follow-up periods, eventually descending to lower BMD levels than women free of breast cancer. To the best of the authors' knowledge, this is the first study of middle-aged women to show a crossover-effect from high to low BMD in longitudinal data of breast cancer incidence compared to controls. And yet, mean BMD over ten annual visits for each group of cases and controls were almost identical, 1.04434 g/cm^2 and 1.04154 g/cm^2, respectively, a difference of only 0.0028 g/cm^2. This small difference highlights the advantage of including random effects in the linear regression model to reveal otherwise hidden rate differences in BMD decline between the two groups.

Higher BMD at baseline suggests that middle-aged women who reported breast cancer during the study had progressed through an earlier stage of increased BMD deposition in the years before enrollment in the SWAN cohort. The cohort data does not show the maximum BMD levels attained by these women before enrollment, nor does it show when incidence of excessive mineralization may have occurred in these women, perhaps coinciding with increasing effects of phosphate toxicity associated with declining renal function. Renal function tends to decrease with advancing age, which is "a normal biological phenomenon linked to cellular and organ senescence" (297), and renal function "seems to diminish with menopause" (298).

The model also shows that BMD in women who self-reported incidence of breast cancer over 10 years was already in decline from the beginning of the annual visits. Furthermore, this finding rules out the effect of cancer treatment on bone loss in women before breast cancer incidence was reported. Additionally, decline in BMD during follow-up visits rules out the effect of HRT that increases BMD while increasing cancer risk. However, although women were not taking hormones in the three months prior to enrollment in the cohort (201), HRT cannot be ruled out as a factor contributing to increased BMD and increased cancer risk before enrollment in women reporting breast cancer in follow-up visits.

Longitudinal data used in the present model helps mitigate study design issues and divergent findings in previous studies of BMD in breast cancer. Perhaps the strongest evidence associating the model findings with dysregulated phosphate and phosphate toxicity is the recent 2022 case-control study showing that women with breast cancer had higher BMD despite having low vitamin D levels (241). Higher vitamin D levels are normally associated with healthy BMD, and lower vitamin D levels are associated with dysregulated phosphate metabolism as the kidneys reduce calcitriol levels to lower intestinal phosphate absorption. This evidence supports the abnormal nature of elevated BMD associated with dysregulated phosphate metabolism.

Integration of the foregoing qualitative and quantitative evidence in the MM-GT study (i.e., evidence from the grounded theory and the SWAN longitudinal cohort study, respectively) supports the findings that a greater magnitude of changes in BMD over time are associated with breast cancer incidence in the SWAN cohort. Furthermore, this association shares associations with phosphate toxicity and dysregulated Pi sequestered in the tumor microenvironment that stimulates breast cancer incidence (20). Overall, findings of the present study have implications for bone metastasis in metastatic breast cancer involving dysregulated phosphate metabolism and phosphate toxicity, and more studies are needed in this area. Importantly, the SWAN cohort data doesn't contain biomarkers of phosphate toxicity associated with bone mineral disorders, such as altered levels of serum phosphate, calcium, PTH, and FGF23 (299), and follow-up studies are needed to test the role of dysregulated phosphate metabolism and phosphate toxicity as mediating factors in the association of bone mineral density changes in breast cancer. Figure 10 integrates BMD changes and breast cancer in the SWAN cohort, potentially associated with dysregulated serum Pi and phosphate toxicity.

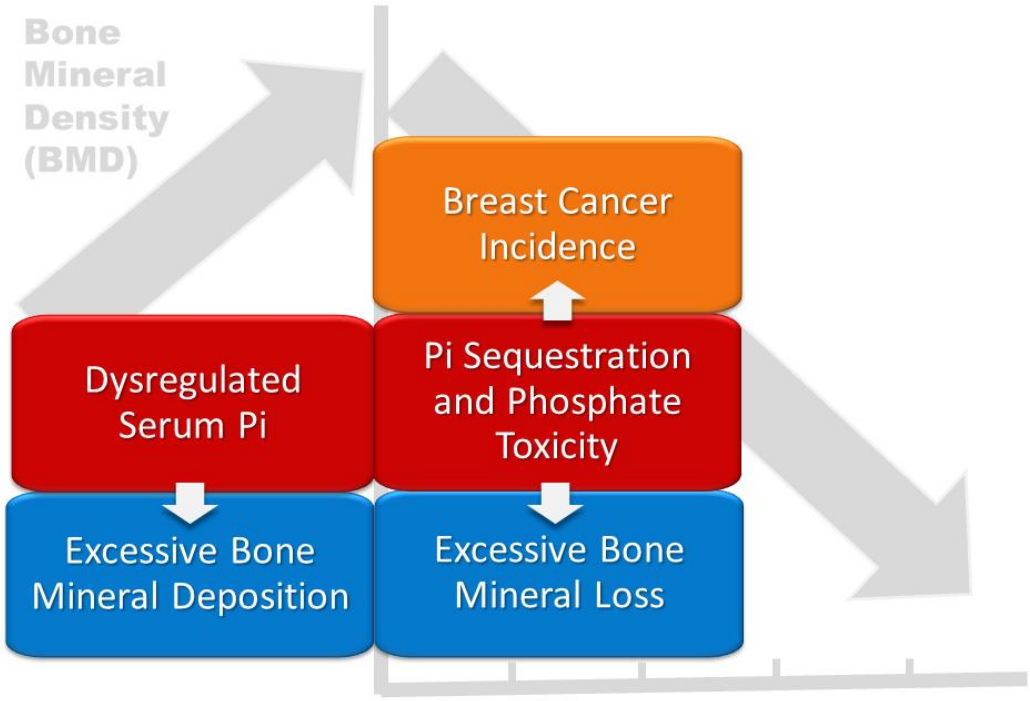

Figure 12. Breast cancer and longitudinal changes in BMD potentially associated with dysregulated serum Pi and phosphate toxicity in the SWAN cohort.

Limitations of this study include the lack of additional biomarkers linking breast cancer, bone mineral density, and dysregulated phosphate metabolism. For example, future studies should include vitamin D levels and levels of other endocrine hormones that regulate Pi metabolism, as well as estimated glomerular filtration rates related to renal regulation of phosphate metabolism. Another confounding effect could have occurred from medications that increased BMD in the SWAN cohort. As previously mentioned, healthy BMD is neither excessively high or low (300). Although protective effects from increases in BMD caused by cancer drugs like tamoxifen are "debatable" (301), any effects from cancer drugs on BMD are ruled out in Study 3 because none of the women had or received treatment for breast cancer at enrollment. Neither were any women receiving hormone replacement therapy at the time of enrollment, which also rules out increased BMD from drug effects (247). Additionally, responses from women in the cohort self-reporting cancer diagnoses or treatment may be subject to information bias

due to participant errors in recall. Additionally, the associations described in this study are not clinical proof of causation, and more research is needed to confirm proposed pathophysiological mechanisms relating breast cancer and bone mineral density. Nevertheless, results of the present MM-GT study may lead to future clinical investigations of dysregulated phosphate metabolism and phosphate toxicity as causes of bone metastasis in incurable metastatic breast cancer. Importantly, "unraveling the biology that governs the interplay between breast neoplastic cells and bone tissue would provide means for the development of new therapeutic agents" (284), including low-phosphate dietary interventions.

Findings in this study can inform development of clinical applications aiming to prevent or reverse the promotion and progression (metastasis) of breast cancer through nutritional interventions that lower patients' intake of dietary phosphate. Furthermore, restoration and maintenance of normal serum phosphate levels in patients can be assisted with pharmacotherapies such as phosphate binders that reduce intestinal absorption of dietary phosphorus (302). Limitations of these clinical applications include the need for trained personnel to instruct, monitor, and guide patients to follow dietary interventions. Patient adherence is also poor for oral administration of phosphate binders (303), and these medications can be expensive. Fortunately, low-phosphate diets that are safe and effective are already in use for patients with CKD (304). Applying an interdisciplinary approach, renal dietitians trained to guide CKD patients to adhere to low-phosphate diets could be employed in feasibility studies to test the hypothesis that a daily low-phosphate diet (800–1000 mg (259)) will help reduce abnormal bone mineral changes and tumor size in breast cancer patients. Clinical results could be monitored through medical imaging of affected bone and breast tissue within the tumor microenvironment.

5.6 Conclusions

In the present MM-GT study, a grounded theory literature-review method was used to synthesize findings of the research literature, leading to a hypothesis positing that a greater magnitude of changes in BMD over time are associated with breast cancer in middle-aged women. A mixed-effects linear regression model based on the SWAN cohort confirmed that longitudinal BMD changes were higher in women self-reporting breast cancer but declined at a faster pace than BMD changes in women without breast cancer. Future clinical studies are needed to further investigate the causative role of dysregulated phosphate and phosphate toxicity in BMD abnormalities and bone metastasis in

metastatic breast cancer. Furthermore, the authors previously found that high dietary phosphate intake was associated with increased breast cancer risk in the SWAN cohort, and a low-phosphate dietary intervention should be tested to reduce abnormal bone mineral density changes and tumorigenesis in breast cancer patients. Future studies should also monitor endocrine hormonal levels that regulate phosphate metabolism, as well as bio-indicators of decreasing renal function.

Chapter 6

General discussion

Global incidence of breast cancer is predicted to continue to increase over the coming decades (2), yet the long history of failed attempts to cure cancer with pharmacotherapies aimed at killing cancer cells is not encouraging (305). Furthermore, alternative medicine that replaces standard medical care with treatments for cancer using special diets, herbal remedies, vitamin supplements, etc., lack randomized clinical trials to prove efficacy (306).

"Sensitive, specific, easily available, and cost-effective diagnostic and therapeutic approaches are urgently required for the reduction of breast cancer incidence and prevalence" (2). As an example of an alternative or adjunct to standard oncological treatments, Schipper et al. proposed a research model in which cancer growth may be controlled through metabolic regulatory processes (149). This cancer regulatory model is based on five principles, paraphrased as follows:

1. Cancer evolves from normal cells as they adapt to the cell microenvironment.
2. The non-malignant portion of the cancer cell continues to function in a normal manner.
3. Cancer evolves from dysregulated metabolism, not from cell autonomy.
4. The dysregulation process may be reversible.
5. Killing cancer cells harms the host response and may exacerbate the dysregulation process, resulting in reoccurrences and secondary tumors.

Clearly, based on the findings of the present thesis, tumorigenesis associated with phosphate toxicity from excessive amounts of dysregulated phosphate sequestered within the tumor microenvironment fulfills the biological conditions predicted by the cancer regulatory model described above by Schipper et al. For example, evidence from Study 1 implicates phosphate toxicity from rhabdomyolysis and renal burden as a plausible mediating factor in the association of alcohol consumption with breast cancer risk. With further investigations to confirm this relationship, this new knowledge could strengthen the public health message for women to reduce risk of breast cancer by limiting alcohol intake. Also, in Study 2, the clinically significant finding of increased relative risk of breast cancer associated with dietary phosphate levels approximating USDA menu recommendations is important new knowledge that requires further investigations. Furthermore, the findings of bone

mineral abnormalities associated with breast cancer risk in Study 3 can open up new avenues for research on metastatic breast cancer and phosphate toxicity.

Other research findings of phosphate toxicity consistent with Schipper et al.'s cancer regulatory model include the present author's review on cancer cachexia and phosphate toxicity (224) in which the author proposed that tumorigenesis potentially provides a means of protecting body tissue by sequestering harmful levels of circulating Pi. Evidence for this proposal is provided by findings of phosphate-related declines in longevity and severe pathophysiological effects in the skeletal system of mice that overexpress tumor-suppression gene P53 and develop no tumors in comparison with tumorigenesis in normal wildtype mice. Additional evidence is provided by the dangerous rapid release of Pi into the serum of patients during tumor lysis syndrome resulting from aggressive treatments that destroy tumors (307). Proposed protection from circulating phosphate toxicity afforded by tumor sequestration could also help explain tumor evasion (protection) from destructive effects imposed by the immune system (308).

Failure to address the root cause of tumorigenesis with strategies that modify dietary phosphate intake and lower phosphate concentrations in the tumor microenvironment could also account for the metastatic recurrence of tumors and secondary tumors following conventional treatments (309). Further research in these areas of cancer biology could eventually explain therapeutic failures in the misguided attempt to kill cancer cells instead of removing cellular exposure to phosphate toxicity in the tumor microenvironment that is responsible for overstimulating cellular proliferation.

6.1 Nutrient Toxicity

A common theme running throughout this thesis is the toxic property of the essential nutrient phosphorus, which appears to be an anomaly in nutrition. For example, in their review of excessive dietary phosphate and cancer, Arnst and Beck Jr. described the "paradox" of how an essential nutrient like phosphorus can cause tumorigenesis (48). The stealth nature of dietary phosphorus as a potential carcinogen appears to have eluded the attention of nutritional epidemiology researchers in investigations of dietary causes of cancer. Yet in a 1981 article in *Nutrition Reviews*, Campbell et al. explained how nutrients become toxic with excessive consumption (310). Spanning across a dose-response curve, an intake of a nutrient ranges from deficiency to adequacy to toxicity. For example, the gradual transition from an essential nutrient to a carcinogen explains the curvilinear association of increasing dietary phosphate intake levels with risk for breast cancer in Study 2 of this thesis.

Importantly, Campbell et al. explained that recommended nutrient guidelines were originally intended to help reduce deficiency diseases, but the public realizes that other diseases may occur with excessive consumption of nutrients and dietary factors such as salt, sugar, fat, calories, and cholesterol (310). However, the authors also explained that the public is much less aware of potential harmful health effects from consuming an excess of vitamins and minerals. Furthermore, Campbell et al. pointed out that even though consuming a sudden megadose of a nutrient may have immediate acute toxic effects, more concerning is unawareness of "chronic nutrient toxicity where the effects develop more subtly and slowly" (310). For example, the association of phosphorus with breast cancer in amounts over 1800 mg, demonstrated in Study 2 of this thesis, are well below the tolerable upper intake level of a 4000-mg megadose of phosphate (22). This may account for the difficulty in identifying phosphate as a primary carcinogenic agent when consumed in amounts approximately equivalent to USDA recommendations.

To the best of the present author's knowledge, no tumor has yet to be identified that lacks an excess of intracellular phosphate in cancer cells, and future research could potentially identify phosphorus as the singular most essential carcinogen among all declared carcinogens. For example, many other carcinogens appear to be associated with tumorigenesis by impairing renal function (311, 312), which increases dysregulated phosphate metabolism. Such a mediating mechanism could explain why so many substances, such as alcohol in Study 1 of this thesis, appear to be carcinogenic at first, but are indirectly associated with tumorigenesis through mediation by phosphate toxicity. Furthermore, alcohol may be the tip of the iceberg, and this mediating mechanism warrants investigations with other carcinogenic substances.

6.2 A Novel Interdisciplinary Grounded Theory Methodology

A point consistently raised throughout the proposal, defense, and revision of the present thesis is that the GT literature-review method lacks the effectiveness of conventional grounded theory and appears to be nothing more than a standard narrative literature review. This section more fully explains how the novel application of GT in the present thesis introduces a new methodology for interdisciplinary research. The application of this new methodology is certainly different from the conventional GT approach, but it is just as powerful and effective to provide new knowledge. The difference in methodologies lies in the perspective of new knowledge obtained. For example, an introspective vertical perspective to gain in-depth knowledge of a defined subject area is obtained by using

conventional GT. On the other hand, a novel extrospective horizontal perspective using GT can facilitate interdisciplinary investigations that synthesize knowledge spanning across separate and unrelated subject areas. The comparative analysis and iterative induction methods are the same in both conventional GT and extrospective GT for interdisciplinary research—the main difference is the source of data used.

Interdisciplinary research is needed to innovate more effective treatments and interventions in clinical and population-based cancer research, but the disadvantages of current interdisciplinary research include lack of an evidence-based methodology, in addition to high risk of project failure, high expense, and lengthy time periods (313). “Making the methods of interdisciplinary research more transparent, and sharing them among researchers, could further invigorate interdisciplinary research” (314).

Applying an extrospective GT approach as a novel method for interdisciplinary research in cancer has potential to help achieve breakthrough knowledge through interdisciplinary findings. This was demonstrated in the present thesis. For example, Study 1 used an extrospective interdisciplinary GT method to synthesize concepts from the fields of oncology, toxicology, nutritional epidemiology, and breast cancer biology to propose that the association of alcohol and breast cancer is mediated by nontraumatic rhabdomyolysis, hyperphosphatemia, and phosphate toxicity. A similar extrospective GT synthesis of interdisciplinary concepts from osteology and oncology was used in Study 3, which proposed that phosphate toxicity mediates bone mineral disorders with breast cancer. More research is needed using extrospective GT for interdisciplinary research in breast cancer, and the present author plans to publish more papers sharing this innovative methodology in the near future.

6.3 Limitations, Advantages, and Future Research

The main limitation of the epidemiological findings in the present thesis is that the study findings do not demonstrate clinical causation. More importantly, the purpose of the thesis is to demonstrate associations of phosphate toxicity with risk of breast cancer and point the direction for further research in this neglected area of public health. Therefore, a strategy going forward focuses on employing randomized clinical trials to test and translate research findings from the present thesis into novel therapeutic and preventative approaches to manage breast cancer. An advantage of findings in this document and other publications on cancer and phosphate toxicity is that a strong rationale can be presented to support grant applications that fund future clinical investigations.

If future research confirms that breast cancer and associated comorbidities are nutritional-related diseases associated with phosphate toxicity from dietary sources, as the proposed thesis implies, then modifying patients' dietary phosphate intake and alcohol consumption may be plausible methods to control phosphate dysregulation underlying these pathologies. Implementing a low-phosphorus nutrition intervention to treat cancer patients and associated comorbidities is potentially less expensive, less invasive, safer, and may prove clinically effective. Furthermore, preventing these diseases by removing or modifying the common pathophysiological determinant through nutrition interventions may prove useful as a complementary or alternative therapy to oncological treatments.

One particular advantage of this novel approach is that a similar low-phosphate nutritional intervention is already in use by registered dietitians who specialize in renal dietetics to help chronic kidney disease patients manage hyperphosphatemia, and the intervention has demonstrated its clinical safety and effectiveness in treating chronic kidney disease (304). Based upon the evidence presented in this paper, the safety and effectiveness of a low-phosphate nutrition intervention to treat cancer patients and patients with associated comorbidities like bone mineral disorders is plausible and should be tested in pre-clinical studies and eventually in randomized controlled clinical trials (315).

Examples of study designs for future clinical research on dietary phosphate restriction and breast cancer could include feasibility projects and other pre-clinical studies to test the interest and practicality of recruiting patients with breast cancer to participate in a novel dietary intervention. The intervention could be administered with the assistance of renal dietitians trained in guiding patients on low-phosphate diets. In particular, the low-phosphate dietary intervention's effect on reducing bone disorders in breast cancer patients could lead to a new approach in treating and preventing metastatic breast cancer, the deadliest form of breast cancer with no known effective treatment. Other studies could combine the low-phosphate dietary intervention with a variety of onco-therapeutic strategies (chemotherapy, surgery, radiation, etc.) to test if the intervention improves patient outcomes. Eventually, a diet that effectively reduces excessive levels of phosphate could be introduced to the general public as a novel recommendation to effectively reduce the risk of developing breast cancer and other cancers. Findings of the thesis contribute to the literature on phosphate toxicity as an etiologic determinant in tumorigenesis and associated bone disorders. These findings will lead to further studies on prevention of cancer and associated comorbidities through dietary modification of phosphate intake and reduced alcohol consumption to prevent phosphate toxicity leading to breast cancer incidence.

6.3.1 Phosphate Toxicity and Comorbid Kidney Disease in Breast Cancer

This section provides additional evidence supporting the association of phosphate toxicity with breast cancer. Dysregulation of phosphate metabolism is associated with kidney pathology (24, 25), and kidney pathology is among the risk factors associated with breast cancer (31). Thus, breast cancer and kidney disease potentially share dysregulated phosphate metabolism as a common pathophysiological determinant. Chronic kidney disease is so strongly associated with cancer that a transdisciplinary medical specialty evolved to study a link between nephrology and oncology, onco-nephrology (150, 151). Prevalence of chronic kidney disease at time of cancer diagnosis was reported as 12% to 53%, and glomerular filtration was reduced in 50–60% of cancer patients (GFR< 90 mL/min/1.73 m^2) (152), leading to recommendations for a comprehensive onco-nephrological examination in cancer patients to evaluate disturbances in electrolytes, including phosphate.

Kidney vulnerability to nephrotoxic injury is increased from exposure to exogenous toxins and drugs (153). Importantly, "nephrotoxicity is a common adverse effect of many chemotherapeutic agents"(316). Dysregulated metabolism and electrolyte disorders also increase patient vulnerability to renal toxicity, and a significant number of patients are also vulnerable to chronic kidney disease caused by phosphate nephropathy. Note that hypophosphatemia also commonly occurs in cancer patients as a serious complication. Hypophosphatemia is associated with various conditions such as malnutrition from inadequate dietary phosphate intake, adverse therapy effects of chemotherapy drugs, critical illness with poor intestinal phosphate absorption, or a large transcellular Pi shift, including rapid Pi absorption by growing malignancies in tumor genesis syndrome (154).

6.3.2 Statins, Breast Cancer, and Phosphate Toxicity

Another area for future research involves the controversial association of statin therapy with both increased and decreased cancer risk, which is potentially mediated by non-traumatic rhabdomyolysis, similar to the effect of rhabdomyolysis from alcohol in Study 1. Statins are used therapeutically to reduce hypercholesterolemia and reduce the risk of atherosclerotic cardiovascular disease, but adverse effects of statins include risk of rhabdomyolysis from muscle cell damage (317). Additionally, cytotoxic effects of statins inhibit cancer cell proliferation, and statins are associated with reduced risk of breast cancer and other cancers (318). Breast cancer patients who used statins had more favorable outcomes compared to nonusers (319). Yet other studies have shown that statins are carcinogenic (320).

The indication to prescribe statins to reduce hypercholesterolemia and prevent atherosclerosis is likely a confounding factor biasing the association of statins with cancer prevention (321), which is potentially explained by an established inverse association between incidence of cancer and atherosclerosis (28). For example, compared to high-phosphate diets that have been shown to increase cancer risk, atherogenic dietary patterns contain higher amounts of cholesterol which raise serum cholesterol levels and indicate the need for statin therapy. But because dietary fats contain no phosphorus, atherogenic dietary patterns also tend to be lower in overall phosphate, thus lowering cancer risk while increasing risk of atherosclerosis. Therefore, although prescribed statin therapy appears to lower cancer risk, this could be due to confounding by indication from consuming a diet that is high in cholesterol and lower in phosphate. Furthermore, serum is exposed to excessive levels of Pi that could increase cancer risk as rhabdomyolysis induced by statins releases Pi from muscle breakdown, similar to the tumorigenic effect of rhabdomyolysis potentially induced by alcohol described in Study 1. More research is warranted to resolve the controversy of statin therapy in the cause and prevention of breast cancer and other cancers. Lastly, the following manuscript by the author is in preparation for publication, Statins in the Cause and Prevention of Cancer: Confounding by Indication and Mediation by Rhabdomyolysis and Phosphate Toxicity.

6.3.3 Regression and Reversion of Breast Cancer with a Low-Phosphate Diet

Regression and reversion of tumors is an exciting subject area warranting further investigations, particularly involving the role of reduced dietary phosphate overload. Tumors that spontaneously disappear from unknown causes in idiopathic tumor regression (322), and that return to normal cells in tumor reversion (323), are documented phenomena with potential to contribute new knowledge and novel therapies for breast cancer and other cancer patients. The present thesis described how tumorigenesis is associated with dysregulated phosphate metabolism and increased transport of phosphate into tumor cells, potentially mediated by phosphate overload from excessive dietary phosphate intake, which is a common characteristic of the Western diet. Additional evidence from animal studies suggests that reversing this process by reducing dietary phosphate overload and reregulating phosphate metabolism may target and reverse kinase activation of cancer cell signaling and cellular proliferation (34, 324), This could subsequently activate cancer cell self-digestion in autophagy (325) and stimulate tumor regression and reversion. A lower intake of dietary phosphate also may account for tumor regression resulting from sickness-associated anorexia in fevers and acute infections (322). Lower dietary intake of phosphate may also explain tumor regression from low-

calorie diets that mimic fasting (326) and from high-fat ketogenic diets that are low in phosphate (327). Clinical research is needed to test the hypothesis that reducing phosphate overload reverses cancer cell signaling, reduces cellular proliferation in breast cancer patients, and stimulates autophagy of cancer cells in tumors.

Interestingly, cases of spontaneous regression are most often found for melanomas, lymphomas, renal cell carcinomas, neuroblastomas, and testicular malignancies, and less often found for lung and breast cancers (328). However, according to Papac, lower reporting of spontaneous regression of tumors of the breast occurs because breast cancer is so often treated with conventional therapies (329). Reducing dietary phosphate overload in patients with breast cancer has the potential to provide a safe and effective reversion therapy that reverses cancer in cells without killing the cells, and further clinical research is warranted to test tumor reversion therapy (330). Importantly, testing a low-phosphate diet as a neoadjuvant pretreatment for breast cancer reversion therapy avoids impairment of kidney function subsequent to treatment with chemotherapy which could compromise renal reregulation of phosphate metabolism.

Finally, reversion therapy for breast cancer and other cancers is consistent with Schipper et al.'s prediction that dysregulated metabolism in cancer cells is reversible. The potential to return cancer cells to normal cells using a low-phosphate diet in cancer reversion therapy is an exciting prospect for future research.

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Appendices

Appendix A

Categorized Breast Cancer Cases

SWANID	BRSTCAN	DTTKCAL0	DTTKCAL5	DTTKCAL9	DTTPHOS0	DTTPHOS5	DTTPHOS9	AVGKCAL	AVGPHOS	PhosDENS	StdPHOS	SortPHOS	n	Legend
11211	1	793.76	869.0533	1014.13	631.35	904.87086	993.97	892.31	843.40	0.95	1890.36	769.53	n = 2	imputed
13122	1	2072.34	2919.98	2117.39	1168.75	1579.24	979.1	2369.90	1242.36	0.52	1048.45	789.44		SWANID = Participant ID#
15691	1	2177.36	1114.36	477.1539	1204.03	522.4	-21.5919	1256.29	568.28	0.45	904.69	854.65	n = 6 (800-1000)	BRSTCAN = Self-reported breast cancer (1-yes, 0-no)
16265	1	2011.46	1678.56	1441.34	1680.81	1849.6259	1320.435	1710.45	1616.96	0.95	1890.68	862.75		DTTKCAL = Caloric intake at visits 0, 5, 9
19889	1	970.12	1378.06	1358.62	516.09	716.81	817.22	1235.60	683.37	0.55	1106.14	885.68		DTTPHOS = Phosphorus intake at visits 0, 5, 9
20095	1	1304.99	2031.81	746.77	656.75	1238.74	594.54	1361.19	830.01	0.61	1219.54	904.69		
20745	1	967.17	1318.63	944.01	813.16	797.85	821.61	1076.60	810.87	0.75	1506.35	944.40		
22323	1	2169.64	1295.4	1299.27	1158.04	909.07721	1286.907	1588.10	1118.01	0.70	1407.98	999.41		
22878	1	1564.18	1193.14	1297.43	882.5	894.56	814.4	1351.58	863.82	0.64	1278.23	1022.78		
22886	1	1388.79	1988.791	1936.691	602.07	1740.7029	1645.911	1771.42	1329.56	0.75	1501.12	1023.19	n = 13 (>1000-1200)	
24089	1	2108.76	1491.59	2323.65	1306.144	1539.09	1958.76	1974.67	1601.33	0.81	1621.88	1032.46		
25038	1	2289.1	1966.88	1468.37	1822.6	1148.44	900.85	1908.12	1290.63	0.68	1352.78	1048.45		
25175	1	2936.61	1013.42	2221.37	1378.9	473.39	784.9	2057.13	879.06	0.43	854.65	1063.51		
27347	1	1503.8	1473.25	1234.18	1293.52	1220.43	568.43	1403.74	1027.46	0.73	1463.89	1063.94		
27473	1	1965.97	1823.05	1529.76	1377	1327.7	838.19	1772.93	1180.96	0.67	1332.22	1098.53		
28364	1	1443.09	1313.54	1003.29	717.48	859.15	992.44	1253.31	856.36	0.68	1366.56	1101.37		
29481	1	2085.21	2045.26	2470.56	1684.38	1804.95	1788.79	2200.34	1759.37	0.80	1599.18	1105.36		
29741	1	1997.33	1692.32	1306.39	1110.28	880.91	666.55	1665.35	885.91	0.53	1063.94	1106.14		
33309	1	1685.65	1791.84	1224.07	1390.34	1526.38	778.31	1567.19	1231.68	0.79	1571.83	1120.65		
34365	1	1031.05	1827.776	671.2234	664.38	1000.0772	343.8233	1176.68	669.43	0.57	1137.82	1137.82		
36602	1	1823.64	2119.21	1462.66	1672.98	2065.8687	1821.89	1801.84	1853.58	1.03	2057.43	1163.53		
37699	1	2458.56	2279.23	2005.87	1064.63	1277.15	1028.07	2247.89	1123.28	0.50	999.41	1201.13		
37866	1	2766.4	2252.53	2401.92	1900.94	1326.7	1834.43	2473.62	1687.36	0.68	1364.28	1213.37		
38218	1	1832.86	1302.79	1672.61	957.71	843.39	846.74	1602.75	882.61	0.55	1101.37	1219.54		
38720	1	2173.26	915.55	1690.024	1107.67	721.24	1207.946	1592.94	1012.29	0.64	1270.96	1231.88		
39698	1	1423.32	2054.453	1662.078	728.55	866.90146	621.7404	1713.28	739.06	0.43	862.75	1242.97		
41559	1	1179.81	1644.27	1247.19	1240.21	1925.8	1280.98	1357.09	1482.33	1.09	2184.57	1267.30	n = 20 (>1200-1400)	
42594	1	1002.6	1165.39	725.4319	1048.71	1086.84	642.9082	964.47	926.15	0.96	1920.53	1270.96		
44872	1	1566.6	1847.86	1560.62	1225.72	1530.53	1188.49	1658.36	1314.91	0.79	1585.80	1273.44		
44941	1	1514.63	1440.029	1141.126	742.24	1215.3898	1320.385	1365.26	1092.67	0.80	1600.68	1278.23		
45137	1	1380.2	1328.34	1577.55	1268.85	1209.98	1619.8	1428.70	1366.21	0.96	1912.53	1286.51		
48311	1	1595.9	1725.11	1205.27	1412.62	928.2	868.36	1508.76	1069.73	0.71	1418.02	1287.81		
48525	1	1490.29	1150.12	1139.09	1079.79	1016.98	950.58	1259.83	1015.78	0.81	1612.57	1291.85		
48852	1	1803.07	3207.65	2460.57	1071.47	2111.85	1642.57	2490.43	1608.63	0.65	1291.85	1292.57		
49177	1	4086.36	1057.15	1629.21	1836.3	627.68	1000.917	2257.57	1154.97	0.51	1023.19	1299.71		
49658	1	2033.09	2126.67	1336.24	889.28	837.45	442.64	1832.00	723.12	0.39	789.44	1304.09		
50868	1	2230.85	1757.82	1364.58	1198.7	1122.43	893.84	1784.42	1071.66	0.60	1201.13	1332.22		
54639	1	2621.08	1916.118	1420.83	904.4893	787.37627	600.57	1986.01	764.15	0.38	769.53	1340.38		
54919	1	847.73	1339.21	1094.7	591.91	1131.31	920.23	1093.88	881.15	0.81	1611.05	1352.78		
57209	1	883.4	1155.27	818.03	599.8	857.79	381.86	952.23	613.15	0.64	1287.81	1364.28		
57297	1	1310.82	1348.269	1246.293	754.55	1041.0237	750.913	1301.79	848.83	0.65	1304.09	1366.56		
57334	1	2061.32	1987.31	1971.66	1294.56	1321.71	1296.05	2006.76	1304.11	0.65	1299.71	1401.25		
58995	1	2474.52	3422.55	1164.3	1707.647	1982.67	873.33	2353.79	1521.22	0.65	1292.57	1407.98		
60701	1	2148.43	2280.948	1519.098	1088.51	1339.435	905.1369	1982.83	1111.03	0.56	1120.65	1415.91		
60873	1	2204.8	1613.06	1767.48	1390.82	1191.61	1371.75	1861.78	1318.06	0.71	1415.91	1418.02		
64571	1	1379.58	1564.7	1237.46	986.79	1060.46	882.59	1393.91	976.61	0.70	1401.25	1418.77		
67316	1	1514.15	1693.76	1726.37	1075.7	1370.1	1321.34	1644.76	1255.71	0.76	1526.93	1424.45		
67797	1	1229.21	1394.641	1174.865	803.29	647.85872	992.3914	1266.24	814.51	0.64	1286.51	1463.89	n = 14 (>1400-1600)	
68732	1	900.95	1942.19	2100.006	667.69	1683.81	1838.027	1647.72	1396.51	0.85	1695.09	1501.12		
68840	1	876.78	551.9467	624.3438	497.43	233.49897	360.8007	684.36	363.91	0.53	1063.51	1506.35		
69497	1	1419.4	1639.56	1534.97	943.8	1503.7932	1638.768	1531.31	1362.12	0.89	1779.03	1526.93		
71595	1	1206.6	1655.851	1007.111	944.36	1395.3928	1246.505	1289.85	1195.42	0.93	1853.57	1538.47		
71849	1	2822.16	2008.81	1806.22	1558.36	1182.46	1120.46	2212.40	1287.09	0.58	1163.53	1571.83		
72189	1	1013.77	1044.885	1010.165	500.51	1300.8505	1287.601	1022.94	1029.65	1.01	2013.13	1585.80		
75626	1	1291.87	1324.8	1025.5	959.19	1262.65	802.55	1214.06	1008.13	0.83	1660.76	1599.18		
77954	1	1556.47	1735.99	1899.688	1313.29	1711.26	1582.515	1730.72	1535.69	0.89	1774.63	1600.68		
80407	1	1856.62	2429.569	1538.997	1172.75	1012.883	565.025	1941.73	916.89	0.47	944.40	1611.05		
81061	1	3397.28	2802.803	2532.883	2107.52	1670.4658	1520.184	2910.99	1766.06	0.61	1213.37	1612.57		
81364	1	1477.67	1682.56	1695.635	672.77	842.17	968.3092	1618.62	827.75	0.51	1022.78	1621.88		
81677	1	2366.85	1022.98	1539.782	1389.01	600.22	1314.559	1643.20	1101.26	0.67	1340.38	1660.76	n = 9 (>1600-1800)	
82876	1	1113.91	1208.74	1180.49	795.74	752.8	936.54	1167.71	828.36	0.71	1418.77	1669.52		
87770	1	1331.18	1923.35	1890.06	936.41	2382.25	2035.07	1714.86	1784.58	1.04	2081.30	1695.09		
89740	1	2254.82	2324.73	1504.62	1218.12	1254.12	869.59	2028.06	1113.94	0.55	1098.53	1774.63		
91557	1	2169.46	1735.99	1694.89	1230.13	1047.89	1171.45	1866.78	1149.82	0.62	1231.88	1779.03		
93977	1	2246.75	1596.377	2304.1	1382.71	1330.2752	1201.073	2049.08	1304.69	0.64	1273.44	1853.57		
94309	1	1145.69	1100.12	1458.84	628.18	941.48	1068.89	1234.88	879.52	0.71	1424.45	1890.36		
95364	1	1324.91	1736.02	1547.72	1269.76	1916.11	1521.47	1536.22	1569.11	1.02	2042.83	1890.68		
95767	1	2317.43	1583.62	923.68	1104.73	882.74	503.2	1608.24	830.22	0.52	1032.46	1912.53	n = 10 (>1800)	
95986	1	948.07	1118.2	601.373	529.42	704.89	817.7384	889.21	684.02	0.77	1538.47	1920.53		
97505	1	1833.25	1679.74	1832.57	1366.49	1533.45	1562.32	1781.85	1487.42	0.83	1669.52	2013.13		
98294	1	1438.16	2152.39	749.08	1132.182	1043.9986	520.84	1446.54	899.01	0.62	1242.97	2042.83		
98459	1	3871.1	1327.87	2173.86	1076.96	730.74	1457.28	2457.61	1088.33	0.44	885.68	2057.43		
98644	1	2518.21	1968.25	2390.45	1459.65	1368.73	1529.19	2292.30	1452.52	0.63	1267.30	2081.30		
99888	1	2352.54	2838.34	2900.39	1305.81	1559.11	1606.95	2697.09	1490.62	0.55	1105.36	2184.57		
									1123.98		1384.70			
									average		average			
									327.77		335.70			
									SD		SD			

Appendix B

Categorized Random Controls

SWANID	BRSTCAN	DTTKCAL0	DTTKCAL5	DTTKCAL9	DTTPHOS0	DTTPHOS5	DTTPHOS9	AVGKCAL	AVGPHOS	PhosDENS	StdPHOS		n	Legend
10629	0	3533.24	2566.26	2933.91	1657.17	1286.89	1945.29	3011.14	1629.78	0.54	1082.50	574.81	n = 8	imputed
10801	0	1171.3	1517.28	1062.52	626.56	1065.32	677.5395	1250.37	789.81	0.63	1263.32	683.87		SWANID = Participant ID#
10910	0	2306.01	967.18	1594.94	1814.68	574.72	1085.74	1622.71	1158.38	0.71	1427.71	730.23		BRSTCAN = Self-reported breast cancer (1-yes, 0-no)
11180	0	3900.13	3378.05	2214.08	2387.1	1940.98	1451.983	3164.09	1926.69	0.61	1217.85	759.71		DTTKCAL = Caloric intake at visits 0, 5, 9
11338	0	2306.28	1616.65	1187.31	1216.26	940.44	495.94	1703.41	884.21	0.52	1038.17	776.29		DTTPHOS = Phosphorus intake at visits 0, 5, 9
11481	0	1842.58	1352.32	1179.87	1561.08	1254.44	1201.73	1458.26	1339.08	0.92	1836.55	779.53		
11600	0	2145.04	1561.99	2434.47	1118.61	1007.77	1645.32	2047.17	1257.23	0.61	1228.27	780.23		
11788	0	1310.48	1428.29	1307.42	612.42	529.7	814.75	1348.73	652.29	0.48	967.27	790.02		
12183	0	1077.66	1335.88	829.614	658.96	1309.95	1329.53	1081.05	1099.48	1.02	2034.09	814.44	n = 34 (800-1000)	
12830	0	1912.08	1590.6	1726.33	1062.48	1272.3	1007.25	1743.00	1114.01	0.64	1278.26	868.28		
12907	0	2149.5	2217.5	2164.69	1078.53	1259.465	1239.89	2177.23	1192.63	0.55	1095.55	876.89		
13621	0	1503.24	2267.79	1290.6	638.04	458.0557	634.66	1687.21	576.92	0.34	683.87	880.02		
13956	0	1127.32	1192.8	951.44	784.65	761.89	852.08	1090.52	799.54	0.73	1466.35	892.95		
14334	0	1803.78	2692.5	2078.88	1118.319	1552.97	1417.92	2191.72	1363.07	0.62	1243.84	893.10		
14596	0	1749.89	1164.09	1342.33	838.59	795.02	1457.668	1418.77	1030.43	0.73	1452.56	895.25		
15150	0	1721.91	1683.26	1450.67	1242.95	1703.11	1195.44	1618.61	1380.50	0.85	1705.78	901.90		
15210	0	1438.53	1466.35	841.22	655.17	562.947	408.21	1248.70	542.11	0.43	868.28	906.67		
15976	0	1181.24	1469.67	1038.26	761.76	1123.58	763.95	1229.72	883.10	0.72	1436.25	918.02		
16115	0	1459.84	1149.83	1166.35	784.88	867.2401	691.2333	1258.67	781.12	0.62	1241.18	927.25		
16214	0	1121.92	509.09	950.53	777.55	419.88	882.84	860.51	693.42	0.81	1611.65	931.82		
16365	0	2767.56	2936.56	2623.32	1929.76	1909.1	1754.83	2775.81	1864.56	0.67	1343.44	934.08		
16743	0	1543.85	1117.4	1086.69	745.42	569.86	648.57	1249.31	654.62	0.52	1047.96	934.72		
17288	0	1901.75	2131.48	1641.25	1330.55	1574.479	906.4435	1891.49	1270.49	0.67	1343.37	949.85		
17487	0	1354.7	1176.29	1187.28	797.85	556.54	641.15	1239.42	665.18	0.54	1073.37	954.90		
17851	0	681.85	3111.06	1651.48	617.16	2150.5	1148.607	1814.80	1305.42	0.72	1438.64	962.66		
18151	0	1972.25	1935.73	2154.88	930	998.0424	990.1888	2020.96	972.74	0.48	962.66	965.10		
18165	0	1902.37	2230.27	1727.14	1537.63	1727.84	1219.592	1953.26	1495.02	0.77	1530.79	965.40		
18189	0	1620.97	2167.99	2036.77	1041.44	1280.62	1331.161	1941.91	1217.74	0.63	1254.17	966.08		
18414	0	1313.51	1252.55	1247.76	1233.58	131.55	1515.46	1271.27	960.20	0.76	1510.61	967.27		
19474	0	1475.52	1152.2	1444.05	1400.18	1387.29	1799.73	1357.26	1529.07	1.13	2253.17	974.14		
19650	0	2121.02	1960.99	1585.97	1385.56	1082.82	837.36	1889.33	1101.91	0.58	1166.46	976.13		
20047	0	2514.6	1629.51	1044.26	1581.72	1022.03	1041.019	1729.46	1214.92	0.70	1404.98	977.54		
20663	0	919.13	1502.55	650.063	720.83	1015.72	207.0605	1023.91	647.87	0.63	1265.48	977.69		
21532	0	2427.24	1389.56	1821.59	1661.26	1095.71	1570.23	1879.46	1442.40	0.77	1534.91	979.01		
21760	0	2163.26	1845.61	1577.08	2040.45	1660.33	1922.46	1861.98	1874.41	1.01	2013.35	982.47		
21778	0	964.97	2399.4	2167.07	845.04	1155.103	507.4523	1843.81	835.87	0.45	906.67	982.86		
22142	0	1793.5	2290.72	2372.79	1306.88	2035.2	1529.3	2152.34	1623.79	0.75	1508.87	987.01		
22364	0	2245.71	1164.24	1718.17	921.12	756.9521	965.1443	1709.37	881.07	0.52	1030.87	987.87		
22534	0	1936.04	1309.36	1679.52	1126	806.94	991.4	1641.64	974.78	0.59	1187.57	990.50		
22724	0	2461	2080.03	2452.83	1616.3	1244.14	1648.32	2331.29	1502.92	0.64	1289.35	992.18		
23186	0	1272.27	1889.79	1194.92	428.95	726.62	544.15	1452.33	566.57	0.39	780.23	992.55		
23205	0	1693.3	990.492	929.584	1213.36	745.8499	825.9178	1204.46	928.38	0.77	1541.57	993.73		
23445	0	2776.34	2646.53	3897.32	1210.25	1790.461	2068.83	3106.73	1689.85	0.54	1087.86	1006.49		
23459	0	2087.61	1759.29	1972.32	1226.96	1178.89	1172.39	1939.74	1192.75	0.61	1229.80	1009.95		
23805	0	2102.38	1596.4	1641.69	1450.04	1191.13	1219.11	1780.16	1286.76	0.72	1445.67	1011.83		
24170	0	888.8	1789.43	502.65	384.92	839.113	385.2232	1060.29	536.42	0.51	1011.83	1016.14		
24223	0	2490.84	2850.43	2490.84	1790.43	1458.737	1073.43	2610.70	1440.87	0.55	1103.81	1016.67		
24239	0	2355.3	1903.89	2048.85	1050.88	1085.6	1303.13	2102.68	1146.54	0.55	1090.55	1017.87		
24736	0	1308.15	2076.32	1138.85	636.88	1011.97	565.34	1507.77	738.06	0.49	979.01	1019.77		
25090	0	1093.05	2811.84	1544.25	610.95	1323.56	754.66	1816.38	896.39	0.49	987.01	1022.53	n = 58 (>1000-1200)	
25107	0	2053.37	1197.61	1125.92	850.55	629.35	930.8	1458.97	803.57	0.55	1101.56	1026.13		
25389	0	1726.35	1658.44	1918.23	1215.21	1692.13	1566.824	1767.67	1491.39	0.84	1687.40	1030.10		
25959	0	1141.51	1206.24	1115.03	674.22	941.81	607.93	1154.26	741.32	0.64	1284.49	1030.87		
26109	0	1106.75	841.42	672.76	606.83	389.53	601.3	873.64	532.55	0.61	1219.16	1033.33		
26305	0	1866.32	1510.8	1736.46	1597.83	1269.53	1336.546	1704.52	1401.30	0.82	1644.21	1038.17		
26812	0	1435.23	1735.49	1934.04	648.1	1024.182	1148.413	1701.59	940.23	0.55	1105.12	1043.05		
27070	0	1516.7	1800.55	2443.79	1351.47	1363.09	1576.801	1920.35	1430.45	0.74	1489.79	1043.86		
27442	0	1747.25	1341.57	1692.07	635.92	908.067	1321.822	1593.63	955.27	0.60	1198.86	1047.96		
27455	0	920.29	1175.64	1071.64	503.24	583.42	573.86	1055.86	553.51	0.52	1048.45	1048.29		

SWANID	BRSTCAN	DTTKCAL0	DTTKCAL5	DTTKCAL9	DTTPHOS0	DTTPHOS5	DTTPHOS9	AVGKCAL	AVGPHOS	PhosDENS	StdPHOS		n	Legend
27455	0	920.29	1175.64	1071.64	503.24	583.42	573.86	1055.86	553.51	0.52	1048.45	1048.29		
27552	0	1914.39	1241.71	1177.32	944.55	975.92	749.8	1444.47	890.09	0.62	1232.41	1048.45		
28147	0	2705.39	1641	2383.01	1616.51	1102.03	1944.98	2243.13	1554.51	0.69	1386.01	1059.74		
28341	0	1268.33	1029.14	892.04	684.5	566.69	486.35	1063.17	579.18	0.54	1089.53	1061.77		
28616	0	1330.56	1412.77	1334.21	742.98	655.63	674.14	1359.18	690.92	0.51	1016.67	1073.37		
28778	0	2414.91	1984.81	1729.24	1169.79	814.13	759.57	2042.99	914.50	0.45	895.25	1076.43		
28895	0	1272.86	2182.8	1921.3	754.55	1081.848	1388.28	1792.32	1074.89	0.60	1199.44	1082.50		
29059	0	3403.06	1307.79	2345.44	1659.89	1258.375	2097.779	2352.10	1672.01	0.71	1421.72	1083.73		
29084	0	1588.88	1433.47	1795.69	1126.5	1121.8	1520.11	1606.01	1256.14	0.78	1564.29	1085.19		
30395	0	1237.36	1169.15	711.456	792.2	358.2904	381.7774	1039.32	510.76	0.49	982.86	1087.86		
31012	0	1879.2	2098.1	3092.18	1557.91	1529.724	2393.91	2356.49	1827.18	0.78	1550.76	1089.53		
31237	0	1595.28	1597.17	1288.21	1206.39	1229.22	925.4752	1493.55	1120.36	0.75	1500.26	1090.55		
31546	0	2009.85	1037.43	1435.02	1008.39	450.01	636.45	1494.10	698.28	0.47	934.72	1093.50		
31557	0	1480.65	1276.54	914.51	883.69	817.9	654.86	1223.90	785.48	0.64	1283.57	1095.55		
31837	0	3713.31	1353.96	1656.49	3356.88	1163.07	1304.13	2241.25	1941.36	0.87	1732.39	1097.12		
32118	0	1914.97	1481.12	1446.95	1133.48	1345.37	1721.02	1614.35	1399.96	0.87	1734.39	1101.56		
32476	0	2167.98	1159.31	2095.64	1442.59	513.022	1507.784	1807.64	1154.47	0.64	1277.32	1103.81		
33185	0	882.82	1061.41	1177.85	715.43	798.18	927.42	1040.69	813.68	0.78	1563.72	1104.00		
33276	0	2457.1	2671.62	2592.56	1377.77	1452.16	1481.16	2573.76	1437.03	0.56	1116.68	1105.12		
33521	0	4057.09	2030.19	2310.76	1525.21	1186.467	1613.742	2799.35	1441.81	0.52	1030.10	1116.68		
33533	0	1762.57	1312.02	932.15	1006.48	772.51	583.72	1335.58	787.57	0.59	1179.37	1120.61		
33890	0	1982.66	1539.84	1063.51	1132.88	782.82	753.36	1528.67	889.69	0.58	1164.00	1121.92		
34146	0	1578.99	1136.37	1545.79	865.66	543.98	647.21	1420.38	685.62	0.48	965.40	1128.44		
34183	0	1635.45	1621.48	1975.03	986.32	1040.216	1031.247	1743.99	1019.26	0.58	1168.88	1146.91		
34659	0	2371.71	2741.69	2838.69	1475.59	1615.23	1976.819	2650.70	1689.21	0.64	1274.54	1148.59		
34677	0	1047.71	1723.9	1412.51	798.84	802.5829	797.9832	1394.71	799.80	0.57	1146.91	1149.34		
35326	0	1594.5	1194.48	1841.75	1167.32	1136.09	2106.58	1543.58	1470.00	0.95	1904.66	1153.55		
35328	0	1119.57	1032.51	-324.558	784.06	604.28	14.54103	609.17	467.63	0.77	1535.28	1162.28		
35613	0	1831.12	1063.48	1201.36	865.66	784.5559	760.0935	1365.32	803.44	0.59	1176.92	1164.00		
35770	0	1543.86	2341.47	1947.63	944.32	1408.45	1206.67	1944.32	1186.48	0.61	1220.46	1164.72		
35795	0	2406.37	1320.79	1674.6	1190.74	1088.373	1344.512	1800.59	1207.87	0.67	1341.65	1166.46		
35955	0	933.52	1342.36	1258.31	532.83	686.96	575.83	1178.06	598.54	0.51	1016.14	1168.88		
36018	0	646.353	1522.1	1227.52	20.79272	945.73	9.497948	1131.99	325.34	0.29	574.81	1176.92		
36311	0	1604.97	1100.61	847.27	878.54	629.58	556.59	1184.28	688.24	0.58	1162.28	1179.37		
36766	0	2722.6	1883.06	1468.82	2144.95	1435.321	1577.188	2024.83	1719.15	0.85	1698.07	1182.49		
37296	0	2979.88	664.24	1990.95	1885.78	622.54	2152.83	1878.36	1553.72	0.83	1654.34	1185.77		
37373	0	1958.77	2113.16	2123.03	1349.91	1479.961	1067.476	2064.99	1299.12	0.63	1258.23	1187.57		
37479	0	1846.16	2599.01	2439.65	1081.76	1782.91	1626.12	2294.94	1496.93	0.65	1304.55	1188.09		
37599	0	2026.39	1325.89	1608.88	1069.38	995.98	1113.59	1653.72	1059.65	0.64	1281.54	1192.29		
37947	0	1984.26	1473.21	1134.73	1503.33	1311.35	773.91	1530.73	1196.20	0.78	1562.91	1193.93		
38138	0	1926.62	1503.45	2079.48	1028.73	1253.981	1822.805	1836.52	1368.51	0.75	1490.33	1198.86		
38786	0	1533.19	1044.14	1999.88	1071.77	981.29	1771.391	1525.74	1274.82	0.84	1671.08	1199.44		
39056	0	2228.71	2634.81	3118.24	1348.97	1897.21	2034.414	2660.59	1760.20	0.66	1323.17	1200.18		
39278	0	1752.15	1389.63	1817.31	1264.54	1055.23	1408.46	1653.03	1242.74	0.75	1503.59	1200.73		
39528	0	2085.1	1951.4	1931.71	1437.37	1060.186	1986.448	1989.40	1494.67	0.75	1502.63	1208.56		
39819	0	1721.76	1720.8	1918.18	1043.09	1517.52	1541.21	1786.91	1367.27	0.77	1530.32	1209.46		
40044	0	2410.27	2536.67	1866.82	1234.07	1684.334	1172.332	2271.25	1363.58	0.60	1200.73	1210.24		
40131	0	1276.81	1035.67	1153.03	660.33	874.88	846.34	1155.17	793.85	0.69	1374.43	1217.85		
40877	0	2268.62	1829.29	2756.29	1370.93	2107.912	2370.07	2284.73	1949.64	0.85	1706.67	1219.12		
41581	0	1362.12	2817.82	1628.89	817.25	1550.01	784.5944	1936.28	1050.62	0.54	1085.19	1219.16		
41657	0	1849.63	1404.92	1446	1076.44	637.3	1719.4	1566.85	1144.38	0.73	1460.74	1220.46		
42150	0	2237.32	1910.4	2370.78	1557.09	1502.315	1726.84	2172.83	1595.41	0.73	1468.51	1221.11		
42362	0	1434.87	1149.17	1263.59	1083.63	1183.19	1048	1282.54	1104.94	0.86	1723.05	1225.09		
42521	0	1310.29	2478.89	2066.03	658.02	864.292	1212.32	1951.74	911.54	0.47	934.08	1225.66		
42713	0	2120.05	1948.61	1956.75	1586.2	1767.92	1495.95	2008.47	1616.69	0.80	1609.87	1226.50		
42891	0	2383.14	2068.2	2345.23	1626.15	1111.475	1484.318	2265.52	1407.31	0.62	1242.37	1228.12		
42976	0	2519.09	2018.51	2573.85	1372.91	1267.184	1443.963	2370.48	1361.35	0.57	1148.59	1228.27		
43170	0	1349.96	1303.09	1275.33	630.11	814.9751	605.25	1309.46	683.45	0.52	1043.86	1228.46		
43324	0	2244.17	3958.24	3596.73	1383.72	1818.44	1451.69	3266.38	1551.28	0.47	949.85	1229.80		
43505	0	2137.94	2026.65	1557.73	1088.73	1348.13	863.64	1907.44	1100.17	0.58	1153.55	1232.41		
44230	0	1431.8	1604.71	1777.53	1539.15	1288.3	1995.276	1604.68	1607.58	1.00	2003.61	1243.84		

SWANID	BRSTCAN	DTTKCAL0	DTTKCAL5	DTTKCAL9	DTTPHOS0	DTTPHOS5	DTTPHOS9	AVGKCAL	AVGPHOS	PhosDENS	StdPHOS		n	Legend
44230	0	1431.8	1604.71	1777.53	1539.15	1288.3	1995.276	1604.68	1607.58	1.00	2003.61	1243.84		
44395	0	1648.66	1144.8	1326.53	1208.61	1187.02	904.46	1373.33	1100.03	0.80	1601.99	1244.53		
45072	0	1564.92	1978.53	1501.69	790.4	1068.02	714.01	1681.71	857.48	0.51	1019.77	1246.63		
45196	0	3044.94	2160.78	3077.96	1888.38	1442.988	1823.265	2761.22	1718.21	0.62	1244.53	1248.94		
45210	0	3058.71	1938.34	2738.03	2400.57	1941.358	3516.43	2578.36	2619.45	1.02	2031.88	1254.17	n = 93 (>1200-1400)	
45689	0	1666.56	1862.83	2303.79	1175.54	1474.873	1999.35	1944.39	1549.92	0.80	1594.25	1258.23		
45746	0	2916.33	2547.06	2194.81	1588.73	1507.718	1194.478	2552.73	1430.31	0.56	1120.61	1259.19		
46094	0	1732.65	1731.28	1253.74	1157.07	984.115	978.3043	1572.55	1039.83	0.66	1322.47	1263.11		
46254	0	2354.84	1909.99	1627.43	1081.39	1523.699	1519.307	1964.08	1374.80	0.70	1399.94	1263.32		
47423	0	1416.05	1323.39	1519.07	677.81	640.96	848.54	1419.50	722.44	0.51	1017.87	1265.48		
47595	0	1238.14	3148.94	2008.66	1141.38	1926.43	1356.39	2131.91	1474.73	0.69	1383.48	1267.96		
47789	0	2815.54	1775.27	1671.86	1401.79	979.57	1217.6	2087.56	1199.65	0.57	1149.34	1268.84		
47805	0	1387.85	1438.54	1529.24	664.84	713.57	1404.611	1451.88	927.67	0.64	1277.90	1272.47		
47844	0	1436.17	1278.73	1272.13	1154.35	912.21	749.15	1329.01	938.57	0.71	1412.43	1274.34		
48041	0	1132.92	1058.83	1663.68	621.6	304.0696	795.6802	1285.14	573.78	0.45	892.95	1274.54		
48104	0	2398.48	1793.74	1803.7	1517.27	1371.95	1546.15	1998.64	1478.46	0.74	1479.46	1277.25		
48491	0	2179.04	2113.07	1758.99	1094.39	1471.4	1090.77	2017.03	1218.85	0.60	1208.56	1277.32		
48515	0	1658.99	1898.31	2010.81	1088.93	1858.92	1044.803	1856.04	1330.88	0.72	1434.11	1277.90		
48532	0	2566.76	3330.9	2646.1	1496.34	1915.79	1856.5	2847.92	1756.21	0.62	1233.33	1278.26		
49252	0	2228.75	2201.78	2378.71	2128.42	1650.324	2007.869	2269.75	1928.87	0.85	1699.63	1281.54		
49618	0	1190.69	1823.99	1352.18	639.76	826.8634	228.3632	1455.62	565.00	0.39	776.29	1283.51		
49770	0	2350.11	1502.46	1665.79	1072.33	963.89	1688.67	1839.45	1241.63	0.67	1350.00	1283.57		
49850	0	2732.74	2437.1	1748.78	1498.19	1363.71	1578.17	2306.21	1480.02	0.64	1283.51	1284.49		
50183	0	1781.53	1772.96	1579.53	1050.24	1543.268	1422.111	1711.34	1338.54	0.78	1564.32	1286.52		
50997	0	1277.87	1566.41	845.83	702.83	1329.78	733.79	1230.04	922.13	0.75	1499.36	1287.26		
51582	0	1670.23	1032.11	1014.53	991.16	917.7075	1003.202	1238.96	970.69	0.78	1566.94	1288.40		
51641	0	2307.49	2245.47	1702.15	1461.21	1277.65	1046.228	2085.04	1261.70	0.61	1210.24	1288.44		
51878	0	2221.39	1572.3	2413.58	1687.45	1082.55	2425.66	2069.09	1731.89	0.84	1674.06	1289.35		
52487	0	1574.86	1461.69	1400.43	794.19	851.5947	1285.084	1478.99	976.96	0.66	1321.11	1296.15		
52503	0	1654.53	1616.22	1027.86	839.79	766.62	487.32	1432.87	697.91	0.49	974.14	1300.53		
53185	0	2024.71	2832.91	2836.09	1161.25	2200.95	1518.84	2564.57	1627.01	0.63	1268.84	1304.55		
53287	0	1205.6	657.281	780.002	850.88	464.236	633.1281	880.96	649.41	0.74	1474.33	1305.29		
53438	0	2115.65	2253.1	2119	1399.53	662.6848	1035.37	2162.58	1032.53	0.48	954.90	1306.32		
53669	0	1900.12	2476.26	1838.6	709.29	1375.43	999.62	2071.66	1028.11	0.50	992.55	1316.65		
53899	0	1551.38	1135.27	2627.06	970.49	736.85	1531.68	1771.24	1079.67	0.61	1219.12	1317.99		
53945	0	1394.21	1601.24	1208.87	653.89	585.44	295.7363	1401.44	511.69	0.37	730.23	1321.11		
54054	0	1325.92	1376.02	1226.31	955.27	495.2977	753.0129	1309.42	734.53	0.56	1121.92	1321.17		
54996	0	1835.5	1551.48	1495.62	1396.08	693.53	665.24	1627.53	918.28	0.56	1128.44	1321.79		
56433	0	969.91	710.092	969.91	819.97	744.8476	960.79	883.30	841.87	0.95	1906.18	1322.47		
56821	0	1921.58	1412.72	1367.61	1309.08	1239.64	915.53	1567.30	1154.75	0.74	1473.55	1323.17		
56838	0	1247.01	1690.7	1704.56	1462.14	2080.67	1660.35	1547.42	1734.39	1.12	2241.64	1328.17		
56880	0	2620.3	2713.06	3208.74	1114.16	1429.5	1982.56	2847.37	1508.74	0.53	1059.74	1334.41		
58648	0	3338.99	3351.17	2171.7	1480.14	1405.73	1242.977	2953.95	1376.28	0.47	931.82	1341.23		
58837	0	2344.76	2421.11	1202.67	1501.8	1897.69	980.16	1989.51	1459.88	0.73	1467.58	1341.46		
58906	0	2131.85	1641.01	1522.4	1395.74	1170.95	1084.28	1765.09	1216.99	0.69	1378.96	1341.65		
59427	0	1500.16	1849.54	1322.02	804.43	883.6361	792.071	1557.24	826.71	0.53	1061.77	1343.37		
59740	0	774.35	610.87	933.32	565.37	595.13	1110.46	772.85	756.99	0.98	1958.96	1343.44		
60495	0	1978.46	1579.9	2212.15	1546.05	1081.63	1928.849	1923.50	1518.84	0.79	1579.25	1350.00		
60504	0	1841.21	1008.16	1390.03	681.17	497.87	714.06	1413.13	631.03	0.45	893.10	1350.01		
60981	0	1308.73	1436.33	2245.32	860.09	902.87	1626.46	1663.46	1129.81	0.68	1358.38	1350.52		
61564	0	1900.51	1406.34	1055.4	901.09	761.08	612.85	1454.08	758.34	0.52	1043.05	1352.47		
62189	0	1509.07	1491.37	1456.93	1052.02	1358.51	968.06	1485.79	1126.20	0.76	1515.96	1358.38		
62806	0	1694.17	1700.53	1453.64	782.34	1084.57	1013.22	1616.11	960.04	0.59	1188.09	1360.82		
63342	0	1454.63	1398.58	1313.38	1282.23	914	910.95	1388.86	1035.73	0.75	1491.47	1361.12		
63783	0	887.57	2159.34	710.895	425.07	1088.68	455.8864	1252.60	656.55	0.52	1048.29	1361.59		

SWANID	BRSTCAN	DTTKCAL0	DTTKCAL5	DTTKCAL9	DTTPHOS0	DTTPHOS5	DTTPHOS9	AVGKCAL	AVGPHOS	PhosDENS	StdPHOS		n	Legend
63783	0	887.57	2159.34	710.895	425.07	1088.68	455.8864	1252.60	656.55	0.52	1048.29	1361.59		
64716	0	1847.73	1990	1054.48	869.61	1283.117	1301.402	1630.74	1151.38	0.71	1412.09	1362.36		
64754	0	1244.86	225.303	741.069	974.53	596.6557	913.6051	737.08	828.26	1.12	2247.43	1363.41		
64794	0	3468.03	2155.14	2005.12	2048.32	1677.37	1474.56	2542.76	1733.42	0.68	1363.41	1371.67		
65261	0	1335.32	1551.87	2421.99	1023.92	1418.026	1263.017	1769.73	1234.99	0.70	1395.68	1371.72		
65941	0	1843.29	2322.59	2201.62	1790.85	2280.62	1978.69	2122.50	2016.72	0.95	1900.33	1372.85		
66169	0	1231.11	1606.63	1898.51	646.83	1251.106	1325.363	1578.75	1074.43	0.68	1361.12	1374.43		
66677	0	2754.89	1916.11	1778.55	2267.68	1701.376	1691.13	2149.85	1886.73	0.88	1755.22	1377.31		
66739	0	2773.5	1967.05	1926.78	1462.49	1873.878	1467.286	2222.44	1601.22	0.72	1440.95	1378.96		
67010	0	843.96	1728.05	744	737.6	1065.679	284.4578	1105.34	695.91	0.63	1259.19	1383.48		
67011	0	1900.8	822.156	963.111	950.5	639.6073	211.5399	1228.69	600.55	0.49	977.54	1386.01		
67248	0	971.99	74.2408	438.238	698.55	33.12864	545.8761	494.82	425.85	0.86	1721.23	1389.46		
67305	0	971.34	2448.94	2008.96	666.19	1672.793	1045.144	1809.75	1128.04	0.62	1246.63	1391.19		
67432	0	1759.34	1921.39	1801.5	1076.47	1287.5	1501.16	1827.41	1288.38	0.71	1410.06	1391.31		
67827	0	1759.06	2532.45	2244.7	736.14	1083.308	762.4266	2178.73	860.62	0.40	790.02	1394.60		
67961	0	1998.59	1542.04	1858.14	1100.17	1012.78	1203.142	1799.59	1105.36	0.61	1228.46	1395.68		
67996	0	1056.17	2869.86	2660.59	581.7	1829.977	1982.947	2195.54	1464.87	0.67	1334.41	1399.94		
68894	0	1826.45	1397.17	1792.87	1363.22	634.1931	923.996	1672.16	973.80	0.58	1164.72	1400.71		
69343	0	1228.65	784.99	1290.96	712.8	621.4	1125.58	1101.53	819.93	0.74	1488.70	1404.98		
69503	0	2591.48	1182.23	1288.08	1034.02	767.0723	1490.42	1687.26	1097.17	0.65	1300.53	1407.76		
69649	0	1999.99	1625.76	1646.25	1213.95	1073.81	1248.32	1757.33	1178.69	0.67	1341.46	1410.06		
69838	0	2737.46	2077.83	2781.83	1681.18	1503.417	2598.52	2532.37	1927.71	0.76	1522.45	1410.14		
69969	0	1897.69	1416.47	2461.98	1237.88	912.4602	1782.038	1925.38	1310.79	0.68	1361.59	1411.21		
70970	0	2028.64	1272.23	2137.06	1224.3	857.26	1378.25	1812.64	1153.27	0.64	1272.47	1412.09		
71067	0	1078.84	946.97	1031.22	822.33	728.23	714.41	1019.01	754.99	0.74	1481.81	1412.24		
71305	0	1981.92	3189.62	1984.28	1169.52	1403.34	1028.28	2385.27	1200.38	0.50	1006.49	1412.43		
71464	0	1932.92	2229.68	1710.87	1199.47	1386.445	1380.21	1957.83	1322.04	0.68	1350.52	1420.60		
72165	0	1940.01	1807.01	1313.17	1029.46	863.15	1208.42	1686.73	1033.68	0.61	1225.66	1421.72		
72369	0	1524.03	1808.57	1492.27	580.3	807.11	728.03	1608.29	705.15	0.44	876.89	1423.36		
72576	0	3592.93	2837.24	2085.37	1255.54	962.97	1249.19	2838.51	1155.90	0.41	814.44	1427.48		
72702	0	1884.95	1734.21	1795.22	982.35	1018.66	1340.31	1804.79	1113.77	0.62	1234.24	1427.71		
72933	0	1923.69	1854.04	1542.06	1173.25	1349.09	1178.08	1773.26	1233.47	0.70	1391.19	1430.66		
74581	0	1781.83	1824.98	1276.9	1042.88	709.03	876.57	1627.90	876.16	0.54	1076.43	1434.11		
74786	0	3151.92	2590.43	2623.79	1768.53	1411.34	1780.28	2788.71	1653.38	0.59	1185.77	1436.25		
74861	0	3259.83	1177.1	1030.89	2198.03	1197.819	1041.73	1822.61	1479.19	0.81	1623.16	1437.47		
75503	0	1134.15	2240.68	1284.11	573.9	1021.053	795.3879	1552.98	796.78	0.51	1026.13	1438.64		
75529	0	1641.86	2417.52	1462.06	1031.54	1666.46	1092.06	1840.48	1263.35	0.69	1372.85	1440.95		
75543	0	2413.48	1520.11	2163	864.6	714.75	1365.55	2032.20	981.63	0.48	966.08	1445.67		
75761	0	2965.67	2019.47	2758.25	1778.54	1531.653	1964.465	2581.13	1758.22	0.68	1362.36	1452.56		
76366	0	1500.52	1181.25	1372.62	727.43	576.51	710.55	1351.46	671.50	0.50	993.73	1460.28		
76649	0	1698.15	1351.62	1962.21	1294.19	1469.145	1933.571	1670.66	1565.64	0.94	1874.27	1460.74		
76743	0	2749.83	2364.3	1985.92	2379.44	2372.4	1770.74	2366.68	2174.19	0.92	1837.33	1466.35		
77385	0	1454.41	1122.08	1938.89	695.83	890.88	1397.478	1505.13	994.73	0.66	1321.79	1467.58		
77394	0	1448.98	946.65	1695.74	1020.72	770.58	1149.31	1363.79	980.20	0.72	1437.47	1468.51	n = 62 (>1400-1600)	
77776	0	2162.81	1906.09	2635.51	745.28	634.9714	1166.434	2234.80	848.90	0.38	759.71	1472.84		
77809	0	1759.33	1141.39	1450.12	987.32	1007.911	1461.636	1450.28	1152.29	0.79	1589.06	1473.55		
78016	0	1296.63	1074.91	1444.89	828.55	538.1	971.08	1272.14	779.24	0.61	1225.09	1474.33		
78068	0	3851.75	2311.59	2466.25	2272.28	1549.165	2014.17	2876.53	1945.21	0.68	1352.47	1479.46		
78420	0	1199.9	1981.98	1049.43	1369.6	1657.62	1082.635	1410.44	1369.95	0.97	1942.59	1481.81		
78451	0	1322	1043.68	420.522	807.69	729.72	692.437	928.73	743.28	0.80	1600.64	1488.70		
78455	0	1408.23	1022.1	1035.81	964.04	709.72	805.67	1155.38	826.48	0.72	1430.66	1489.79		
78546	0	2055.74	2219.05	2272.51	846.73	949.88	1155.9	2182.43	984.17	0.45	901.90	1490.33		
79043	0	1202.47	2174.52	2135.17	1041.41	1507.07	1202.039	1837.39	1250.17	0.68	1360.82	1491.47		
79727	0	875.11	2244.56	1577.07	543.12	1657.476	864.71	1565.58	1021.77	0.65	1305.29	1499.36		
79954	0	1441.92	1928.95	1577.01	1248.6	1305.36	1058.69	1649.29	1204.22	0.73	1460.28	1500.26		
80157	0	2614.84	2799.83	2269.73	2155.75	2041.88	2127.03	2561.47	2108.22	0.82	1646.10	1502.63		
80653	0	1995.98	1520.52	2002.45	924.59	953.86	1168	1839.65	1015.48	0.55	1104.00	1503.59		
80655	0	1104.36	1793.51	1530.71	705.15	1054.38	1110.532	1476.19	956.69	0.65	1296.15	1508.87		
80761	0	1715.92	1568.69	1673.34	671.81	1041.458	1417.937	1652.65	1043.74	0.63	1263.11	1510.61		
80893	0	1733.62	1237.69	2021.07	1181.15	848.36	1257.09	1664.13	1095.53	0.66	1316.65	1513.57		

SWANID	BRSTCAN	DTTKCAL0	DTTKCAL5	DTTKCAL9	DTTPHOS0	DTTPHOS5	DTTPHOS9	AVGKCAL	AVGPHOS	PhosDENS	StdPHOS		n	Legend
80893	0	1733.62	1237.69	2021.07	1181.15	848.36	1257.09	1664.13	1095.53	0.66	1316.65	1513.57		
81100	0	3222.07	2530.9	1717.21	1257.81	1323.2	847.88	2490.06	1142.96	0.46	918.02	1515.96		
81430	0	2083.34	2646.19	2516.17	1276.2	1378.93	1726.558	2415.23	1460.56	0.60	1209.46	1522.45		
81837	0	2130.46	1914.07	2387.56	1529.93	1519.346	1909.416	2144.03	1652.90	0.77	1541.86	1528.42		
82166	0	1357.22	1874.07	1143.37	644.75	905.71	610.33	1458.22	720.26	0.49	987.87	1530.32		
82255	0	1686.75	1668.24	1463.38	845.53	960.78	804.59	1606.12	870.30	0.54	1083.73	1530.79		
82605	0	2173.31	1589.73	1602.79	1384.49	1112.1	1101.82	1788.61	1199.47	0.67	1341.23	1534.91		
82609	0	1943.01	1981.57	1519.13	992.84	1375.85	898.0146	1814.57	1088.90	0.60	1200.18	1535.28		
82905	0	1716.86	1351.16	1247.37	2318.33	1756.41	1204.87	1438.46	1759.87	1.22	2446.88	1541.57		
83011	0	2145.76	1556.86	2019.23	1314.56	1299.57	1758.556	1907.28	1457.56	0.76	1528.42	1541.86		
83354	0	973.72	1338.15	1088.49	567.8	930.63	747.8	1133.45	748.74	0.66	1321.17	1550.76		
83433	0	1698.61	1757.28	1289.72	861.78	824.39	645.05	1581.87	777.07	0.49	982.47	1552.66		
83953	0	1227.51	1587.44	2189.31	703.77	950.44	1534.349	1668.09	1062.85	0.64	1274.34	1562.91		
84331	0	2324.26	2604.95	3314.06	936.31	1414.47	1678.91	2747.76	1343.23	0.49	977.69	1563.72		
84525	0	1644.36	1548.22	1263.26	740.61	803.8392	705.65	1485.28	750.03	0.50	1009.95	1564.29		
84646	0	1559.26	1804.9	1671.78	861.51	946.52	1169.45	1678.65	992.49	0.59	1182.49	1564.32		
84992	0	3281.78	3149.91	2376.16	1838.14	2652.59	1795.8	2935.95	2095.51	0.71	1427.48	1566.94		
85286	0	912.69	1734.12	2232.46	762.57	945.5891	1204.592	1626.42	970.92	0.60	1193.93	1579.25		
85300	0	2802.2	2222.73	1510.74	1566.66	1614.84	899.82	2178.56	1360.44	0.62	1248.94	1589.06		
85314	0	1401.72	1136.82	1447.16	771.04	780.83	1015.73	1328.57	855.87	0.64	1288.40	1594.25		
85446	0	1491.31	1775.32	1255.93	926.52	1374.37	892.59	1507.52	1064.49	0.71	1412.24	1600.64		
85485	0	1970.34	1624.55	1670.06	1179.64	1069.099	1305.13	1754.98	1184.62	0.68	1350.01	1601.99		
85658	0	1001.86	1330.05	1691.89	435.31	1286.377	1117.525	1341.27	946.40	0.71	1411.21	1609.87		
87042	0	4735.06	3937.08	1979.29	2359.08	1889.33	1254.79	3550.48	1834.40	0.52	1033.33	1611.65		
87166	0	1971.96	2398.08	2071.56	883.1783	1284.906	666.29	2147.20	944.79	0.44	880.02	1623.16		
87205	0	1559.67	1956.48	955.484	1004.05	1284.15	589.88	1490.54	959.36	0.64	1287.26	1626.14		
87737	0	1713.03	1417.19	1619.11	843.85	855.91	896.93	1583.11	865.56	0.55	1093.50	1644.21		
88194	0	2119.69	1676.4	1371.06	827.26	641.3597	545.3534	1722.38	671.32	0.39	779.53	1646.10		
88284	0	1263.81	1536.62	1776.43	724.85	636.2	909.49	1525.62	756.85	0.50	992.18	1654.34		
88436	0	2899.88	852.36	2107.48	1341.81	668.13	2093.931	1953.24	1367.96	0.70	1400.71	1671.08		
88448	0	924.61	1344.86	1240.17	601.93	2039.52	1278.68	1169.88	1306.71	1.12	2233.92	1674.06		
89112	0	2026.84	1503.44	1734.85	1455.87	1100.64	1530.977	1755.04	1362.50	0.78	1552.66	1687.40		
89364	0	1949.93	1769.38	1791.86	1182.44	705.1803	1397.837	1837.06	1095.15	0.60	1192.29	1692.77		
89467	0	1659.5	2023.79	1545.8	913.17	911.67	727.29	1743.03	850.71	0.49	976.13	1698.07	n = 22 (>1600-1800)	
89456	0	1728.13	1578.31	2222.72	969.48	988.25	1849.96	1843.05	1269.23	0.69	1377.31	1699.63		
89581	0	2030.21	2497.07	2340.15	1513.56	1663.274	1656.997	2289.14	1611.28	0.70	1407.76	1705.78		
90243	0	1142.86	1186.94	1044.35	560.01	822.83	756.31	1124.72	713.05	0.63	1267.96	1706.67		
90794	0	1203.11	1602.06	1538.65	622.63	1191.34	1248.72	1447.94	1020.90	0.71	1410.14	1721.23		
91574	0	2352.17	1718.88	2191.49	1237.55	1121.45	1481.497	2087.51	1280.17	0.61	1226.50	1723.05		
91580	0	1145.11	1426.94	993.44	622.69	1045.33	864.55	1188.50	844.19	0.71	1420.60	1732.39		
91710	0	1470.06	874.11	1640.27	912.6	834.4656	1492.568	1328.15	1079.88	0.81	1626.14	1734.39		
92464	0	972.06	2737.18	2469.11	743.26	1669.58	1532.8	2059.45	1315.21	0.64	1277.25	1755.22		
92723	0	1658.16	1863.14	1957.18	984.77	1097.66	1495.895	1826.16	1192.77	0.65	1306.32	1836.55		
93492	0	1580.04	765.74	729.97	975.89	517.69	643.23	1025.25	712.27	0.69	1389.46	1837.33		
93615	0	1950.32	2088.79	1297.22	1580.05	1526.02	932.39	1778.78	1346.15	0.76	1513.57	1842.87		
93727	0	1795.54	1408.57	1493.63	1724.26	1384.67	1219.73	1565.91	1442.89	0.92	1842.87	1874.27		
93998	0	1449.93	1688.91	1028.17	887.44	962.8416	435.5713	1389.00	761.95	0.55	1097.12	1896.99		
94159	0	2170.49	1358.89	1351.95	937.11	1606.31	804.48	1627.11	1115.97	0.69	1371.72	1900.33		
94589	0	1521.49	2304.22	2379.46	1037.26	1623.68	1459.812	2068.39	1373.58	0.66	1328.17	1904.66		
94937	0	1688.08	1498.57	1595.04	1225.99	778.18	1330.11	1593.90	1111.43	0.70	1394.60	1906.18	n = 19 (>1800)	
95398	0	1852.2	1647.97	774.27	1107.91	514.9789	358.85	1424.81	660.58	0.46	927.25	1942.59		
95756	0	1759.53	921.54	1394.93	835.83	711.23	941.57	1358.67	829.54	0.61	1221.11	1958.96		
95757	0	2117.3	2835.82	2155.2	1662.8	1470.85	1231.266	2369.44	1454.97	0.61	1228.12	2003.61		
95760	0	1277.3	1590.06	1590.45	1222.95	1304.32	1700.95	1485.94	1409.41	0.95	1896.99	2013.35		
96121	0	971.57	1130.45	1041.04	721.08	602.3292	233.1887	1047.69	518.87	0.50	990.50	2031.88		
96187	0	4064.45	2742.78	2907.49	1741.02	1419.354	1806.413	3238.24	1655.60	0.51	1022.53	2034.09		
96478	0	1352.06	1935.91	1483.21	1004.75	1273.42	994.07	1590.39	1090.75	0.69	1371.67	2233.92		
97723	0	2651.46	809.67	2717.8	1608.95	833.5	1538.13	2059.64	1326.86	0.64	1288.44	2241.64		
97995	0	2270.18	2378.03	2394.71	956.94	1235.623	1206.013	2347.64	1132.86	0.48	965.10	2247.43		
98030	0	1646.7	2266.25	1811.59	1236.61	1510.323	1327.11	1908.18	1358.01	0.71	1423.36	2253.17		
98106	0	1157.85	710.87	882.98	614.19	634.77	777.45	917.23	675.47	0.74	1472.84	2446.88		
									1152.27		1316.10			
									average		average			
									380.99		294.54			
									SD		SD			

Appendix C

MI Procedure Breast Cancer Cases

Model Information	
Data Set	WORK.IMPORT
Method	FCS
Number of Imputations	25
Number of Burn-in Iterations	20
Seed for random number generator	962454001

FCS Model Specification	
Method	**Imputed Variables**
Regression	DTTKCAL0 DTTKCAL5 DTTKCAL9 DTTPHOS0 DTTPHOS5 DTTPHOS9

Missing Data Patterns								
Group	**DTTKCAL0**	**DTTKCAL5**	**DTTKCAL9**	**DTTPHOS0**	**DTTPHOS5**	**DTTPHOS9**	**Freq**	**Percent**
1	X	X	X	X	X	X	43	58.11
2	X	X	.	X	X	.	9	12.16
3	X	.	X	X	.	X	2	2.70
4	X	.	X	X	.	.	1	1.35
5	X	.	.	X	.	.	15	20.27
6	.	X	X	.	X	X	2	2.70
7	.	.	X	.	.	X	2	2.70

Missing Data Patterns						
	Group Means					
Group	DTTKCAL0	DTTKCAL5	DTTKCAL9	DTTPHOS0	DTTPHOS5	DTTPHOS9
1	1822.341860	1737.145581	1577.644419	1138.855349	1217.360930	1076.758372
2	1854.398889	1306.041111	.	1085.432222	944.501111	.
3	1308.700000	.	1238.395000	1152.165000	.	1407.930000
4	2169.640000	.	1299.270000	1158.040000	.	.
5	1604.994000	.	.	974.232000	.	.
6	.	2457.070000	1743.975000	.	1760.880000	1416.045000
7	.	.	1084.955000	.	.	560.705000

Variance Information (25 Imputations)							
	Variance				Relative	Fraction	
Variable	Between	Within	Total	DF	Increase in Variance	Missing Information	Relative Efficiency
DTTKCAL0	264.857673	6349.830974	6625.282954	67.791	0.043379	0.041714	0.998334
DTTKCAL5	1952.626406	4138.599298	6169.330760	39.236	0.490681	0.335142	0.986772
DTTKCAL9	758.234125	3725.349359	4513.912849	54.59	0.211675	0.176787	0.992978
DTTPHOS0	112.656143	1875.018498	1992.180887	66.26	0.062486	0.059082	0.997642
DTTPHOS5	849.678692	2517.901744	3401.567585	45.833	0.350953	0.263910	0.989554
DTTPHOS9	419.312519	2586.506723	3022.591743	57.776	0.168600	0.145756	0.994204

Parameter Estimates (25 Imputations)								
Variable	**Mean**	**Std Error**	**95% Confidence Limits**		**DF**	**Minimum**	**Maximum**	**Mu0**
DTTKCAL0	1767.901608	81.395841	1605.470	1930.334	67.791	1724.472630	1797.882354	0
DTTKCAL5	1666.381128	78.545087	1507.539	1825.223	39.236	1583.191658	1748.840256	0
DTTKCAL9	1496.121994	67.185660	1361.456	1630.788	54.59	1432.774450	1548.109698	0
DTTPHOS0	1100.324657	44.633854	1011.217	1189.432	66.26	1082.523330	1128.639388	0
DTTPHOS5	1181.157626	58.322959	1063.748	1298.567	45.833	1121.952021	1230.814391	0
DTTPHOS9	1043.390509	54.978102	933.331	1153.450	57.776	996.414219	1073.363483	0

Parameter Estimates (25 Imputations)		
Variable	**t for H0: Mean=Mu0**	**Pr > |t|**
DTTKCAL0	21.72	<.0001
DTTKCAL5	21.22	<.0001
DTTKCAL9	22.27	<.0001
DTTPHOS0	24.65	<.0001
DTTPHOS5	20.25	<.0001
DTTPHOS9	18.98	<.0001

Obs	_Imputation_	BRSTCAN	SWANID	DTTKCAL0	DTTKCAL5	DTTKCAL9	DTTPHOS0	DTTPHOS5	DTTPHOS9
1	1	1	11211	793.76	869.05328804	1014.13	631.35	904.87086385	993.97
2	1	1	13122	2072.34	2919.98	2117.39	1168.75	1579.24	979.1
3	1	1	15691	2177.36	1114.36	477.1538909	1204.03	522.4	-21.59186432
4	1	1	16265	2011.46	1678.5603418	1441.3395566	1680.81	1849.6259127	1320.4354766
5	1	1	19889	970.12	1378.06	1358.62	516.09	716.81	817.22
6	1	1	20095	1304.99	2031.81	746.77	656.75	1238.74	594.54
7	1	1	20745	967.17	1318.63	944.01	813.16	797.85	821.61
8	1	1	22323	2169.64	1295.400277	1299.27	1158.04	909.07720839	1286.9068799
9	1	1	22878	1564.18	1193.14	1297.43	882.5	894.56	814.4
10	1	1	22886	1388.79	1988.7907594	1936.690639	602.07	1740.7028635	1645.9112387
11	1	1	24089	2108.7596276	1491.59	2323.65	1306.143618	1539.09	1958.76
12	1	1	25038	2289.1	1966.88	1468.37	1822.6	1148.44	900.85
13	1	1	25175	2936.61	1013.42	2221.37	1378.9	473.39	784.9
14	1	1	27347	1503.8	1473.25	1234.18	1293.52	1220.43	568.43
15	1	1	27473	1965.97	1823.05	1529.76	1377	1327.7	838.19
16	1	1	28364	1443.09	1313.54	1003.29	717.48	859.15	992.44
17	1	1	29481	2085.21	2045.26	2470.56	1684.38	1804.95	1788.79
18	1	1	29741	1997.33	1692.32	1306.39	1110.28	880.91	666.55
19	1	1	33309	1685.65	1791.84	1224.07	1390.34	1526.38	778.31
20	1	1	34365	1031.05	1827.7758763	671.22343571	664.38	1000.0772301	343.8233472 1
21	1	1	36602	1823.64	2119.2102202	1462.66	1672.98	2065.8686508	1821.89
22	1	1	37699	2458.56	2279.23	2005.87	1064.63	1277.15	1028.07
23	1	1	37866	2766.4	2252.53	2401.92	1900.94	1326.7	1834.43

Obs	_Imputation_	BRSTCAN	SWANID	DTTKCAL0	DTTKCAL5	DTTKCAL9	DTTPHOS0	DTTPHOS5	DTTPHOS9
24	1	1	38218	1832.86	1302.79	1672.61	957.71	843.39	846.74
25	1	1	38720	2173.26	915.55	1690.0244758	1107.67	721.24	1207.9461168
26	1	1	39698	1423.32	2054.4533017	1662.0783782	728.55	866.90146059	621.74043735
27	1	1	41559	1179.81	1644.27	1247.19	1240.21	1925.8	1280.98
28	1	1	42594	1002.6	1165.39	725.4319289	1048.71	1086.84	642.90818993
29	1	1	44872	1566.6	1847.86	1560.62	1225.72	1530.53	1188.49
30	1	1	44941	1514.63	1440.0286922	1141.1255284	742.24	1215.3898184	1320.384614
31	1	1	45137	1380.2	1328.34	1577.55	1268.85	1209.98	1619.8
32	1	1	48311	1595.9	1725.11	1205.27	1412.62	928.2	868.36
33	1	1	48525	1490.29	1150.12	1139.09	1079.79	1016.98	950.58
34	1	1	48852	1803.07	3207.65	2460.57	1071.47	2111.85	1642.57
35	1	1	49177	4086.36	1057.15	1629.210136	1836.3	627.68	1000.9169373
36	1	1	49658	2033.09	2126.67	1336.24	889.28	837.45	442.64
37	1	1	50868	2230.85	1757.82	1364.58	1198.7	1122.43	893.84
38	1	1	54639	2621.0769432	1916.1176885	1420.83	904.4892614	787.376272	600.57
39	1	1	54919	847.73	1339.21	1094.7	591.91	1131.31	920.23
40	1	1	57209	883.4	1155.27	818.03	599.8	857.79	381.86
41	1	1	57297	1310.82	1348.2694612	1246.2934717	754.55	1041.0236902	750.91295378
42	1	1	57334	2061.32	1987.31	1971.66	1294.56	1321.71	1296.05
43	1	1	58995	2474.5151674	3422.55	1164.3	1707.6474892	1982.67	873.33
44	1	1	60701	2148.43	2280.9475387	1519.0983555	1088.51	1339.4350233	905.13685788
45	1	1	60873	2204.8	1613.06	1767.48	1390.82	1191.61	1371.75
46	1	1	64571	1379.58	1564.7	1237.46	986.79	1060.46	882.59

Obs	_Imputation_	BRSTCAN	SWANID	DTTKCAL0	DTTKCAL5	DTTKCAL9	DTTPHOS0	DTTPHOS5	DTTPHOS9
47	1	1	67316	1514.15	1693.76	1726.37	1075.7	1370.1	1321.34
48	1	1	67797	1229.21	1394.6408132	1174.8648019	803.29	647.8587249	992.3913953
49	1	1	68732	900.95	1942.19	2100.0057203	667.69	1683.81	1838.0265729
50	1	1	68840	876.78	551.9466885	624.3438298	497.43	233.4989684	360.8006916
51	1	1	69497	1419.4	1639.5604769	1534.9700748	943.8	1503.7932195	1638.7681977
52	1	1	71595	1206.6	1655.8506882	1007.110756	944.36	1395.3927548	1246.5049243
53	1	1	71849	2822.16	2008.81	1806.22	1558.36	1182.46	1120.46
54	1	1	72189	1013.77	1044.8850191	1010.1652712	500.51	1300.8504997	1287.6010567
55	1	1	75626	1291.87	1324.8	1025.5	959.19	1262.65	802.55
56	1	1	77954	1556.47	1735.99	1899.6876257	1313.29	1711.26	1582.5146529
57	1	1	80407	1856.62	2429.5688534	1538.996741	1172.75	1012.8830134	565.0250411 6
58	1	1	81061	3397.28	2802.8028037	2532.8827303	2107.52	1670.4658065	1520.1838841
59	1	1	81364	1477.67	1682.56	1695.6354877	672.77	842.17	968.3092295
60	1	1	81677	2366.85	1022.98	1539.7821315	1389.01	600.22	1314.5590705
61	1	1	82876	1113.91	1208.74	1180.49	795.74	752.8	936.54
62	1	1	87770	1331.18	1923.35	1890.06	936.41	2382.25	2035.07
63	1	1	89740	2254.82	2324.73	1504.62	1218.12	1254.12	869.59
64	1	1	91557	2169.46	1735.99	1694.89	1230.13	1047.89	1171.45
65	1	1	93977	2246.75	1596.3766256	2304.1003448	1382.71	1330.2751971	1201.0734254
66	1	1	94309	1145.69	1100.12	1458.84	628.18	941.48	1068.89
67	1	1	95364	1324.91	1736.02	1547.72	1269.76	1916.11	1521.47
68	1	1	95767	2317.43	1583.62	923.68	1104.73	882.74	503.2

Obs	_Imputation_	BRSTCAN	SWANID	DTTKCAL0	DTTKCAL5	DTTKCAL9	DTTPHOS0	DTTPHOS5	DTTPHOS9
69	1	1	95986	948.07	1118.2	601.37301437	529.42	704.89	817.73843021
70	1	1	97505	1833.25	1679.74	1832.57	1366.49	1533.45	1562.32
71	1	1	98294	1438.1557879	2152.3895237	749.08	1132.1824651	1043.9986357	520.84
72	1	1	98459	3871.1	1327.87	2173.86	1076.96	730.74	1457.28
73	1	1	98644	2518.21	1968.25	2390.45	1459.65	1368.73	1529.19
74	1	1	99888	2352.54	2838.34	2900.39	1305.81	1559.11	1606.95

Appendix D

MI Procedure Random Controls

Model Information	
Data Set	WORK.IMPORT1
Method	FCS
Number of Imputations	25
Number of Burn-in Iterations	20
Seed for random number generator	713403001

FCS Model Specification	
Method	**Imputed Variables**
Regression	DTTKCAL0 DTTKCAL5 DTTKCAL9 DTTPHOS0 DTTPHOS5 DTTPHOS9

Missing Data Patterns								
Group	**DTTKCAL0**	**DTTKCAL5**	**DTTKCAL9**	**DTTPHOS0**	**DTTPHOS5**	**DTTPHOS9**	**Freq**	**Percent**
1	X	X	X	X	X	X	145	48.99
2	X	X	X	X	X	.	1	0.34
3	X	X	.	X	X	X	1	0.34
4	X	X	.	X	X	.	47	15.88
5	X	X	.	X	.	.	1	0.34
6	X	.	X	X	.	X	20	6.76
7	X	.	.	X	.	.	78	26.35
8	.	X	X	.	X	X	1	0.34
9	.	X	.	.	X	.	1	0.34
10	.	.	X	.	.	X	1	0.34

Missing Data Patterns							
	Group Means						
Group	DTTKCAL0	DTTKCAL5	DTTKCAL9	DTTPHOS0	DTTPHOS5	DTTPHOS9
1	1852.346552	1691.673310	1618.920897	1125.526414	1114.629379	1125.243517
2	3338.990000	3351.170000	2171.700000	1480.140000	1405.730000	.
3	1559.670000	1956.480000	.	1004.050000	1284.150000	589.880000
4	1740.593404	1810.472979	.	1140.624043	1228.607872	.
5	1470.060000	874.110000	.	912.600000	.	.
6	1905.866500	.	1872.876000	1160.119500	.	1345.289500
7	1922.831026	.	.	1128.243846	.	.
8	.	2692.500000	2078.880000	.	1552.970000	1417.920000
9	.	1522.100000	.	.	945.730000	.
10	.	.	2071.560000	.	.	666.290000

Variance Information (25 Imputations)							
	Variance						
Variable	Between	Within	Total	DF	Relative Increase in Variance	Fraction Missing Information	Relative Efficiency
DTTKCAL0	12.712613	1487.348283	1500.569401	290.17	0.008889	0.008817	0.999647
DTTKCAL5	332.345633	1468.403394	1814.042852	174.56	0.235385	0.192973	0.992340
DTTKCAL9	977.485467	1192.422187	2209.007072	66.022	0.852538	0.469481	0.981567
DTTPHOS0	4.591595	651.762934	656.538193	290.7	0.007327	0.007278	0.999709
DTTPHOS5	127.539668	694.708518	827.349773	194.73	0.190931	0.162113	0.993557
DTTPHOS9	579.991524	775.231239	1378.422425	71.19	0.778079	0.446360	0.982459

Parameter Estimates (25 Imputations)								
Variable	Mean	Std Error	95% Confidence Limits		DF	Minimum	Maximum	Mu0
DTTKCAL0	1861.750002	38.737184	1785.509	1937.991	290.17	1854.635540	1870.640796	0
DTTKCAL5	1758.614718	42.591582	1674.554	1842.675	174.56	1715.819760	1796.663554	0
DTTKCAL9	1674.035410	47.000075	1580.197	1767.874	66.022	1610.210621	1724.607591	0
DTTPHOS0	1130.962088	25.623001	1080.532	1181.392	290.7	1126.470102	1136.839327	0

Parameter Estimates (25 Imputations)								
Variable	**Mean**	**Std Error**	**95% Confidence Limits**		**DF**	**Minimum**	**Maximum**	**Mu0**
DTTPHOS5	1151.272392	28.763688	1094.544	1208.001	194.73	1121.455772	1172.625572	0
DTTPHOS9	1155.024168	37.127112	1080.998	1229.050	71.19	1116.386162	1197.711113	0

Parameter Estimates (25 Imputations)		
Variable	**t for H0: Mean=Mu0**	**Pr > |t|**
DTTKCAL0	48.06	<.0001
DTTKCAL5	41.29	<.0001
DTTKCAL9	35.62	<.0001
DTTPHOS0	44.14	<.0001
DTTPHOS5	40.03	<.0001
DTTPHOS9	31.11	<.0001

Obs	_Imputation_	BRSTCAN	SWANID	DTTKCAL0	DTTKCAL5	DTTKCAL9	DTTPHOS0	DTTPHOS5	DTTPHOS9
1	1	0	10629	3533.24	2566.26	2933.91	1657.17	1286.89	1945.29
2	1	0	10801	1171.3	1517.28	1062.5150783	626.56	1065.32	677.53953859
3	1	0	10910	2306.01	967.18	1594.94	1814.68	574.72	1085.74
4	1	0	11180	3900.13	3378.05	2214.0787873	2387.1	1940.98	1451.983168
5	1	0	11338	2306.28	1616.65	1187.31	1216.26	940.44	495.94
6	1	0	11481	1842.58	1352.32	1179.87	1561.08	1254.44	1201.73
7	1	0	11600	2145.04	1561.99	2434.47	1118.61	1007.77	1645.32
8	1	0	11788	1310.48	1428.29	1307.42	612.42	529.7	814.75
9	1	0	12183	1077.66	1335.88	829.61354983	658.96	1309.95	1329.530305
10	1	0	12830	1912.08	1590.6	1726.33	1062.48	1272.3	1007.25
11	1	0	12907	2149.5	2217.5045977	2164.6867692	1078.53	1259.4647306	1239.890286
12	1	0	13621	1503.24	2267.7855888	1290.6	638.04	458.05566219	634.66
13	1	0	13956	1127.32	1192.8	951.44	784.65	761.89	852.08
14	1	0	14334	1803.775277	2692.5	2078.88	1118.3191032	1552.97	1417.92
15	1	0	14596	1749.89	1164.09	1342.3346998	838.59	795.02	1457.6680194
16	1	0	15150	1721.91	1683.26	1450.67	1242.95	1703.11	1195.44
17	1	0	15210	1438.53	1466.3522284	841.22	655.17	562.94704561	408.21
18	1	0	15976	1181.24	1469.67	1038.26	761.76	1123.58	763.95
19	1	0	16115	1459.84	1149.8348235	1166.345783	784.88	867.24012791	691.23334123
20	1	0	16214	1121.92	509.09	950.53	777.55	419.88	882.84
21	1	0	16365	2767.56	2936.56	2623.32	1929.76	1909.1	1754.83
22	1	0	16743	1543.85	1117.4	1086.69	745.42	569.86	648.57
23	1	0	17288	1901.75	2131.4762978	1641.2509678	1330.55	1574.4790357	906.4435213
24	1	0	17487	1354.7	1176.29	1187.28	797.85	556.54	641.15

Obs	_Imputation_	BRSTCAN	SWANID	DTTKCAL0	DTTKCAL5	DTTKCAL9	DTTPHOS0	DTTPHOS5	DTTPHOS9
25	1	0	17851	681.85	3111.06	1651.4806005	617.16	2150.5	1148.6073964
26	1	0	18151	1972.25	1935.7330603	2154.8828768	930	998.04235871	990.18879904
27	1	0	18165	1902.37	2230.27	1727.1424804	1537.63	1727.84	1219.5919634
28	1	0	18189	1620.97	2167.99	2036.767564	1041.44	1280.62	1331.1612764
29	1	0	18414	1313.51	1252.55	1247.76	1233.58	131.55	1515.46
30	1	0	19474	1475.52	1152.2	1444.05	1400.18	1387.29	1799.73
31	1	0	19650	2121.02	1960.99	1585.97	1385.56	1082.82	837.36
32	1	0	20047	2514.6	1629.51	1044.2588193	1581.72	1022.03	1041.019457
33	1	0	20663	919.13	1502.55	650.06271189	720.83	1015.72	207.06054897
34	1	0	21532	2427.24	1389.56	1821.59	1661.26	1095.71	1570.23
35	1	0	21760	2163.26	1845.61	1577.08	2040.45	1660.33	1922.46
36	1	0	21778	964.97	2399.4042829	2167.0656052	845.04	1155.1028121	507.4522849
37	1	0	22142	1793.5	2290.72	2372.79	1306.88	2035.2	1529.3
38	1	0	22364	2245.71	1164.2404672	1718.1680953	921.12	756.95206827	965.14428925
39	1	0	22534	1936.04	1309.36	1679.52	1126	806.94	991.4
40	1	0	22724	2461	2080.03	2452.83	1616.3	1244.14	1648.32
41	1	0	23186	1272.27	1889.79	1194.92	428.95	726.62	544.15
42	1	0	23205	1693.3	990.49173555	929.58416249	1213.36	745.84994609	825.91775167
43	1	0	23445	2776.34	2646.5309805	3897.32	1210.25	1790.4613485	2068.83
44	1	0	23459	2087.61	1759.29	1972.32	1226.96	1178.89	1172.39
45	1	0	23805	2102.38	1596.4	1641.69	1450.04	1191.13	1219.11
46	1	0	24170	888.8	1789.4265435	502.64981274	384.92	839.11298199	385.22319002
47	1	0	24223	2490.84	2850.4272435	2490.84	1790.43	1458.7369659	1073.43

Obs	_Imputation_	BRSTCAN	SWANID	DTTKCAL0	DTTKCAL5	DTTKCAL9	DTTPHOS0	DTTPHOS5	DTTPHOS9
48	1	0	24239	2355.3	1903.89	2048.85	1050.88	1085.6	1303.13
49	1	0	24736	1308.15	2076.32	1138.85	636.88	1011.97	565.34
50	1	0	25090	1093.05	2811.84	1544.25	610.95	1323.56	754.66
51	1	0	25107	2053.37	1197.61	1125.92	850.55	629.35	930.8
52	1	0	25389	1726.35	1658.44	1918.2277788	1215.21	1692.13	1566.8238399
53	1	0	25959	1141.51	1206.24	1115.03	674.22	941.81	607.93
54	1	0	26109	1106.75	841.42	672.76	606.83	389.53	601.3
55	1	0	26305	1866.32	1510.7952649	1736.4594283	1597.83	1269.5296412	1336.5458359
56	1	0	26812	1435.23	1735.4898245	1934.0408673	648.1	1024.1823033	1148.4132017
57	1	0	27070	1516.7	1800.55	2443.7858789	1351.47	1363.09	1576.8009332
58	1	0	27442	1747.25	1341.5686629	1692.0745533	635.92	908.0669714	1321.8220404
59	1	0	27455	920.29	1175.64	1071.64	503.24	583.42	573.86
60	1	0	27552	1914.39	1241.71	1177.32	944.55	975.92	749.8
61	1	0	28147	2705.39	1641	2383.01	1616.51	1102.03	1944.98
62	1	0	28341	1268.33	1029.14	892.04	684.5	566.69	486.35
63	1	0	28616	1330.56	1412.77	1334.21	742.98	655.63	674.14
64	1	0	28778	2414.91	1984.81	1729.24	1169.79	814.13	759.57
65	1	0	28895	1272.86	2182.7982716	1921.3	754.55	1081.8483556	1388.28
66	1	0	29059	3403.06	1307.7891733	2345.4446094	1659.89	1258.3754286	2097.7786248
67	1	0	29084	1588.88	1433.47	1795.6923194	1126.5	1121.8	1520.1103757
68	1	0	30395	1237.36	1169.1510333	711.45591057	792.2	358.29035845	381.77742946
69	1	0	31012	1879.2	2098.0983366	3092.18	1557.91	1529.7243287	2393.91
70	1	0	31237	1595.28	1597.17	1288.2115507	1206.39	1229.22	925.47519867

Obs	_Imputation_	BRSTCAN	SWANID	DTTKCAL0	DTTKCAL5	DTTKCAL9	DTTPHOS0	DTTPHOS5	DTTPHOS9
71	1	0	31546	2009.85	1037.43	1435.02	1008.39	450.01	636.45
72	1	0	31557	1480.65	1276.54	914.51	883.69	817.9	654.86
73	1	0	31837	3713.31	1353.96	1656.49	3356.88	1163.07	1304.13
74	1	0	32118	1914.97	1481.12	1446.95	1133.48	1345.37	1721.02
75	1	0	32476	2167.98	1159.3088647	2095.6392218	1442.59	513.02201512	1507.7837749
76	1	0	33185	882.82	1061.41	1177.85	715.43	798.18	927.42
77	1	0	33276	2457.1	2671.62	2592.56	1377.77	1452.16	1481.16
78	1	0	33521	4057.09	2030.1850895	2310.7599747	1525.21	1186.4666443	1613.7417707
79	1	0	33533	1762.57	1312.02	932.15	1006.48	772.51	583.72
80	1	0	33890	1982.66	1539.84	1063.51	1132.88	782.82	753.36
81	1	0	34146	1578.99	1136.37	1545.79	865.66	543.98	647.21
82	1	0	34183	1635.45	1621.4846984	1975.0321283	986.32	1040.2160073	1031.2474038
83	1	0	34659	2371.71	2741.69	2838.6923991	1475.59	1615.23	1976.8186952
84	1	0	34677	1047.71	1723.9037043	1412.5066523	798.84	802.58285445	797.98323442
85	1	0	35326	1594.5	1194.48	1841.75	1167.32	1136.09	2106.58
86	1	0	35328	1119.57	1032.51	-324.5575223	784.06	604.28	14.5410281 7
87	1	0	35613	1831.12	1063.4824047	1201.3573824	865.66	784.55586115	760.09345171
88	1	0	35770	1543.86	2341.47	1947.63	944.32	1408.45	1206.67
89	1	0	35795	2406.37	1320.7875721	1674.6038941	1190.74	1088.3733059	1344.5115 99
90	1	0	35955	933.52	1342.36	1258.31	532.83	686.96	575.83
91	1	0	36018	646.35269762	1522.1	1227.5243151	20.792722699	945.73	9.4979481208
92	1	0	36311	1604.97	1100.61	847.27	878.54	629.58	556.59
93	1	0	36766	2722.6	1883.0624475	1468.8208515	2144.95	1435.3210996	1577.1883821

Obs	_Imputation_	BRSTCAN	SWANID	DTTKCAL0	DTTKCAL5	DTTKCAL9	DTTPHOS0	DTTPHOS5	DTTPHOS9
94	1	0	37296	2979.88	664.24	1990.9495972	1885.78	622.54	2152.8304795
95	1	0	37373	1958.77	2113.1614691	2123.0295634	1349.91	1479.9607113	1067.4758277
96	1	0	37479	1846.16	2599.01	2439.65	1081.76	1782.91	1626.12
97	1	0	37599	2026.39	1325.89	1608.876376	1069.38	995.98	1113.590407
98	1	0	37947	1984.26	1473.21	1134.73	1503.33	1311.35	773.91
99	1	0	38138	1926.62	1503.4493343	2079.4809176	1028.73	1253.9805044	1822.8052011
100	1	0	38786	1533.19	1044.14	1999.8825309	1071.77	981.29	1771.3912118
101	1	0	39056	2228.71	2634.81	3118.2409754	1348.97	1897.21	2034.4144702
102	1	0	39278	1752.15	1389.63	1817.31	1264.54	1055.23	1408.46
103	1	0	39528	2085.1	1951.4003567	1931.7085345	1437.37	1060.1857292	1986.4483922
104	1	0	39819	1721.76	1720.8	1918.18	1043.09	1517.52	1541.21
105	1	0	40044	2410.27	2536.6738966	1866.8160219	1234.07	1684.3341388	1172.3317497
106	1	0	40131	1276.81	1035.67	1153.03	660.33	874.88	846.34
107	1	0	40877	2268.62	1829.2907464	2756.2878577	1370.93	2107.9123654	2370.0695002
108	1	0	41581	1362.12	2817.82	1628.8916381	817.25	1550.01	784.59439729
109	1	0	41657	1849.63	1404.92	1446	1076.44	637.3	1719.4
110	1	0	42150	2237.32	1910.3977286	2370.78	1557.09	1502.3147361	1726.84
111	1	0	42362	1434.87	1149.17	1263.59	1083.63	1183.19	1048
112	1	0	42521	1310.29	2478.8941306	2066.03	658.02	864.29201844	1212.32

Obs	_Imputation_	BRSTCAN	SWANID	DTTKCAL0	DTTKCAL5	DTTKCAL9	DTTPHOS0	DTTPHOS5	DTTPHOS9
113	1	0	42713	2120.05	1948.61	1956.75	1586.2	1767.92	1495.95
114	1	0	42891	2383.14	2068.2041054	2345.2303841	1626.15	1111.4754819	1484.3175392
115	1	0	42976	2519.09	2018.5114388	2573.8510619	1372.91	1267.18438	1443.9630239
116	1	0	43170	1349.96	1303.0927794	1275.33	630.11	814.9751424	605.25
117	1	0	43324	2244.17	3958.24	3596.73	1383.72	1818.44	1451.69
118	1	0	43505	2137.94	2026.65	1557.73	1088.73	1348.13	863.64
119	1	0	43572	3461.64	1197.7635662	2708.3961429	1846.42	1229.1164045	1663.8730233
120	1	0	43722	2323.55	1705.979594	2784.97	1314.8	1352.0177746	1823.89
121	1	0	43792	1058.49	2376.4817469	1211.4686014	761.43	1502.7442138	968.14243401
122	1	0	44036	2158.13	2317.23	2323.63	1821.95	1856.79	2075.84
123	1	0	44230	1431.8	1604.71	1777.5320966	1539.15	1288.3	1995.2764123
124	1	0	44395	1648.66	1144.8	1326.53	1208.61	1187.02	904.46
125	1	0	45072	1564.92	1978.53	1501.69	790.4	1068.02	714.01
126	1	0	45196	3044.94	2160.7751819	3077.9573779	1888.38	1442.9878857	1823.264793
127	1	0	45210	3058.71	1938.3379235	2738.03	2400.57	1941.3584991	3516.43
128	1	0	45689	1666.56	1862.8315733	2303.79	1175.54	1474.8726126	1999.35
129	1	0	45746	2916.33	2547.0572282	2194.8142834	1588.73	1507.7181306	1194.4777256

Obs	_Imputation_	BRSTCAN	SWANID	DTTKCAL0	DTTKCAL5	DTTKCAL9	DTTPHOS0	DTTPHOS5	DTTPHOS9
130	1	0	46094	1732.65	1731.2769495	1253.7371187	1157.07	984.11503839	978.30426333
131	1	0	46254	2354.84	1909.9853776	1627.4289603	1081.39	1523.6987755	1519.3066897
132	1	0	47423	1416.05	1323.39	1519.07	677.81	640.96	848.54
133	1	0	47595	1238.14	3148.94	2008.6645647	1141.38	1926.43	1356.3896463
134	1	0	47789	2815.54	1775.27	1671.86	1401.79	979.57	1217.6
135	1	0	47805	1387.85	1438.54	1529.2352623	664.84	713.57	1404.6113079
136	1	0	47844	1436.17	1278.73	1272.13	1154.35	912.21	749.15
137	1	0	48041	1132.92	1058.8261449	1663.6813864	621.6	304.06957887	795.68021388
138	1	0	48104	2398.48	1793.74	1803.7	1517.27	1371.95	1546.15
139	1	0	48491	2179.04	2113.07	1758.99	1094.39	1471.4	1090.77
140	1	0	48515	1658.99	1898.31	2010.80885	1088.93	1858.92	1044.8027132
141	1	0	48532	2566.76	3330.9	2646.1	1496.34	1915.79	1856.5
142	1	0	49252	2228.75	2201.7835397	2378.709655	2128.42	1650.3239513	2007.8692374
143	1	0	49618	1190.69	1823.9911234	1352.184128	639.76	826.86340986	228.36315786
144	1	0	49770	2350.11	1502.46	1665.79	1072.33	963.89	1688.67
145	1	0	49850	2732.74	2437.1	1748.78	1498.19	1363.71	1578.17
146	1	0	50183	1781.53	1772.9598134	1579.5345332	1050.24	1543.2679939	1422.1110148

Obs	_Imputation_	BRSTCAN	SWANID	DTTKCAL0	DTTKCAL5	DTTKCAL9	DTTPHOS0	DTTPHOS5	DTTPHOS9
147	1	0	50997	1277.87	1566.41	845.83	702.83	1329.78	733.79
148	1	0	51582	1670.23	1032.1137299	1014.5340589	991.16	917.70749512	1003.2016949
149	1	0	51641	2307.49	2245.47	1702.1518161	1461.21	1277.65	1046.2284636
150	1	0	51878	2221.39	1572.3	2413.58	1687.45	1082.55	2425.66
151	1	0	52487	1574.86	1461.6861598	1400.4331855	794.19	851.59474621	1285.0835205
152	1	0	52503	1654.53	1616.22	1027.86	839.79	766.62	487.32
153	1	0	53185	2024.71	2832.91	2836.09	1161.25	2200.95	1518.84
154	1	0	53287	1205.6	657.28070598	780.00176619	850.88	464.23603823	633.12808828
155	1	0	53438	2115.65	2253.1003749	2119.0027335	1399.53	662.68476007	1035.3703326
156	1	0	53669	1900.12	2476.26	1838.6	709.29	1375.43	999.62
157	1	0	53899	1551.38	1135.27	2627.06	970.49	736.85	1531.68
158	1	0	53945	1394.21	1601.24	1208.8659954	653.89	585.44	295.73631441
159	1	0	54054	1325.92	1376.0207843	1226.3069881	955.27	495.29768298	753.01293926
160	1	0	54996	1835.5	1551.48	1495.62	1396.08	693.53	665.24
161	1	0	56433	969.91	710.09167168	969.91	819.97	744.84760577	960.79
162	1	0	56821	1921.58	1412.72	1367.61	1309.08	1239.64	915.53
163	1	0	56838	1247.01	1690.7	1704.56	1462.14	2080.67	1660.35

Obs	_Imputation_	BRSTCAN	SWANID	DTTKCAL0	DTTKCAL5	DTTKCAL9	DTTPHOS0	DTTPHOS5	DTTPHOS9
164	1	0	56880	2620.3	2713.06	3208.74	1114.16	1429.5	1982.56
165	1	0	58648	3338.99	3351.17	2171.7	1480.14	1405.73	1242.9769897
166	1	0	58837	2344.76	2421.11	1202.67	1501.8	1897.69	980.16
167	1	0	58906	2131.85	1641.01	1522.4	1395.74	1170.95	1084.28
168	1	0	59427	1500.16	1849.5370353	1322.0233217	804.43	883.63612073	792.07101447
169	1	0	59740	774.35	610.87	933.32	565.37	595.13	1110.46
170	1	0	60495	1978.46	1579.9	2212.1494704	1546.05	1081.63	1928.849227
171	1	0	60504	1841.21	1008.16	1390.03	681.17	497.87	714.06
172	1	0	60981	1308.73	1436.33	2245.3205483	860.09	902.87	1626.4597589
173	1	0	61564	1900.51	1406.34	1055.4	901.09	761.08	612.85
174	1	0	62189	1509.07	1491.37	1456.93	1052.02	1358.51	968.06
175	1	0	62806	1694.17	1700.53	1453.64	782.34	1084.57	1013.22
176	1	0	63342	1454.63	1398.58	1313.38	1282.23	914	910.95
177	1	0	63783	887.57	2159.34	710.89471574	425.07	1088.68	455.88638805
178	1	0	64716	1847.73	1989.9989425	1054.4817645	869.61	1283.1165446	1301.4021626
179	1	0	64754	1244.86	225.30252842	741.06886578	974.53	596.65572904	913.60514379
180	1	0	64794	3468.03	2155.14	2005.12	2048.32	1677.37	1474.56

Obs	_Imputation_	BRSTCAN	SWANID	DTTKCAL0	DTTKCAL5	DTTKCAL9	DTTPHOS0	DTTPHOS5	DTTPHOS9
181	1	0	65261	1335.32	1551.8741571	2421.9934813	1023.92	1418.0256149	1263.0165647
182	1	0	65941	1843.29	2322.59	2201.62	1790.85	2280.62	1978.69
183	1	0	66169	1231.11	1606.6309041	1898.5099077	646.83	1251.1056496	1325.3629247
184	1	0	66677	2754.89	1916.107124	1778.5519257	2267.68	1701.3761155	1691.1302264
185	1	0	66739	2773.5	1967.0490754	1926.778394	1462.49	1873.8776651	1467.2855273
186	1	0	67010	843.96	1728.0455734	743.9996102	737.6	1065.6788464	284.4577882
187	1	0	67011	1900.8	822.15592413	963.11130409	950.5	639.60728607	211.53991683
188	1	0	67248	971.99	74.240824408	438.23834766	698.55	33.128640867	545.87610783
189	1	0	67305	971.34	2448.9401843	2008.9631769	666.19	1672.7930023	1045.1435632
190	1	0	67432	1759.34	1921.39	1801.5	1076.47	1287.5	1501.16
191	1	0	67827	1759.06	2532.4476135	2244.6956027	736.14	1083.3083012	762.42655409
192	1	0	67961	1998.59	1542.04	1858.1364175	1100.17	1012.78	1203.141878
193	1	0	67996	1056.17	2869.8559651	2660.5932756	581.7	1829.9773062	1982.9468769
194	1	0	68894	1826.45	1397.1716316	1792.8697578	1363.22	634.19313879	923.99603137
195	1	0	69343	1228.65	784.99	1290.9551048	712.8	621.4	1125.5803487
196	1	0	69503	2591.48	1182.2281231	1288.08	1034.02	767.07228698	1490.42
197	1	0	69649	1999.99	1625.76	1646.25	1213.95	1073.81	1248.32

Obs	_Imputation_	BRSTCAN	SWANID	DTTKCAL0	DTTKCAL5	DTTKCAL9	DTTPHOS0	DTTPHOS5	DTTPHOS9
198	1	0	69838	2737.46	2077.8292759	2781.8307621	1681.18	1503.4169703	2598.5195126
199	1	0	69969	1897.69	1416.4744149	2461.9789664	1237.88	912.46022028	1782.0383989
200	1	0	70970	2028.64	1272.23	2137.06	1224.3	857.26	1378.25
201	1	0	71067	1078.84	946.97	1031.22	822.33	728.23	714.41
202	1	0	71305	1981.92	3189.62	1984.28	1169.52	1403.34	1028.28
203	1	0	71464	1932.92	2229.6843099	1710.8746973	1199.47	1386.4452902	1380.2095126
204	1	0	72165	1940.01	1807.01	1313.17	1029.46	863.15	1208.42
205	1	0	72369	1524.03	1808.57	1492.27	580.3	807.11	728.03
206	1	0	72576	3592.93	2837.24	2085.37	1255.54	962.97	1249.19
207	1	0	72702	1884.95	1734.21	1795.22	982.35	1018.66	1340.31
208	1	0	72933	1923.69	1854.04	1542.06	1173.25	1349.09	1178.08
209	1	0	74581	1781.83	1824.98	1276.9	1042.88	709.03	876.57
210	1	0	74786	3151.92	2590.43	2623.7929794	1768.53	1411.34	1780.2802052
211	1	0	74861	3259.83	1177.098281	1030.89	2198.03	1197.8187521	1041.73
212	1	0	75503	1134.15	2240.6785249	1284.1120226	573.9	1021.0531019	795.38787458
213	1	0	75529	1641.86	2417.52	1462.06	1031.54	1666.46	1092.06
214	1	0	75543	2413.48	1520.11	2163	864.6	714.75	1365.55

Obs	_Imputation_	BRSTCAN	SWANID	DTTKCAL0	DTTKCAL5	DTTKCAL9	DTTPHOS0	DTTPHOS5	DTTPHOS9
215	1	0	75761	2965.67	2019.4717258	2758.2494659	1778.54	1531.6533288	1964.4648648
216	1	0	76366	1500.52	1181.25	1372.62	727.43	576.51	710.55
217	1	0	76649	1698.15	1351.6217984	1962.2059	1294.19	1469.1447855	1933.5708329
218	1	0	76743	2749.83	2364.3	1985.92	2379.44	2372.4	1770.74
219	1	0	77385	1454.41	1122.08	1938.8860585	695.83	890.88	1397.4784589
220	1	0	77394	1448.98	946.65	1695.74	1020.72	770.58	1149.31
221	1	0	77776	2162.81	1906.0876708	2635.5077778	745.28	634.97137607	1166.4341117
222	1	0	77809	1759.33	1141.3935969	1450.1220085	987.32	1007.9114944	1461.6358849
223	1	0	78016	1296.63	1074.91	1444.89	828.55	538.1	971.08
224	1	0	78068	3851.75	2311.5908209	2466.2504229	2272.28	1549.1652068	2014.1697945
225	1	0	78420	1199.9	1981.98	1049.4279617	1369.6	1657.62	1082.6351404
226	1	0	78451	1322	1043.68	420.52224809	807.69	729.72	692.43698855
227	1	0	78455	1408.23	1022.1	1035.81	964.04	709.72	805.67
228	1	0	78546	2055.74	2219.05	2272.51	846.73	949.88	1155.9
229	1	0	79043	1202.47	2174.52	2135.1710331	1041.41	1507.07	1202.0394943
230	1	0	79727	875.11	2244.5609765	1577.07	543.12	1657.4758494	864.71
231	1	0	79954	1441.92	1928.95	1577.01	1248.6	1305.36	1058.69

Obs	_Imputation_	BRSTCAN	SWANID	DTTKCAL0	DTTKCAL5	DTTKCAL9	DTTPHOS0	DTTPHOS5	DTTPHOS9
232	1	0	80157	2614.84	2799.83	2269.7297429	2155.75	2041.88	2127.0304176
233	1	0	80653	1995.98	1520.52	2002.45	924.59	953.86	1168
234	1	0	80655	1104.36	1793.51	1530.7109768	705.15	1054.38	1110.5320382
235	1	0	80761	1715.92	1568.6888545	1673.3354223	671.81	1041.4579659	1417.9374489
236	1	0	80893	1733.62	1237.69	2021.07	1181.15	848.36	1257.09
237	1	0	81100	3222.07	2530.9	1717.21	1257.81	1323.2	847.88
238	1	0	81430	2083.34	2646.1860662	2516.1728504	1276.2	1378.9300596	1726.5583137
239	1	0	81837	2130.46	1914.0718742	2387.5562719	1529.93	1519.3460774	1909.4164184
240	1	0	82166	1357.22	1874.07	1143.37	644.75	905.71	610.33
241	1	0	82255	1686.75	1668.24	1463.38	845.53	960.78	804.59
242	1	0	82605	2173.31	1589.73	1602.79	1384.49	1112.1	1101.82
243	1	0	82609	1943.01	1981.5700588	1519.1272884	992.84	1375.8502567	898.01455884
244	1	0	82905	1716.86	1351.16	1247.37	2318.33	1756.41	1204.87
245	1	0	83011	2145.76	1556.86	2019.2271339	1314.56	1299.57	1758.5557955
246	1	0	83354	973.72	1338.15	1088.49	567.8	930.63	747.8
247	1	0	83433	1698.61	1757.28	1289.72	861.78	824.39	645.05
248	1	0	83953	1227.51	1587.44	2189.3083097	703.77	950.44	1534.3485368

Obs	_Imputation_	BRSTCAN	SWANID	DTTKCAL0	DTTKCAL5	DTTKCAL9	DTTPHOS0	DTTPHOS5	DTTPHOS9
249	1	0	84331	2324.26	2604.95	3314.06	936.31	1414.47	1678.91
250	1	0	84525	1644.36	1548.2247597	1263.26	740.61	803.83915064	705.65
251	1	0	84646	1559.26	1804.9	1671.78	861.51	946.52	1169.45
252	1	0	84992	3281.78	3149.91	2376.16	1838.14	2652.59	1795.8
253	1	0	85286	912.69	1734.1197987	2232.4590952	762.57	945.58913673	1204.591907
254	1	0	85300	2802.2	2222.73	1510.74	1566.66	1614.84	899.82
255	1	0	85314	1401.72	1136.82	1447.1641882	771.04	780.83	1015.7301982
256	1	0	85446	1491.31	1775.32	1255.93	926.52	1374.37	892.59
257	1	0	85485	1970.34	1624.5487784	1670.06	1179.64	1069.0994015	1305.13
258	1	0	85658	1001.86	1330.0535741	1691.8929699	435.31	1286.3769781	1117.5254859
259	1	0	87042	4735.06	3937.08	1979.29	2359.08	1889.33	1254.79
260	1	0	87166	1971.9601043	2398.0763702	2071.56	883.17832664	1284.9064731	666.29
261	1	0	87205	1559.67	1956.48	955.48398844	1004.05	1284.15	589.88
262	1	0	87737	1713.03	1417.19	1619.11	843.85	855.91	896.93
263	1	0	88194	2119.69	1676.3978119	1371.0615332	827.26	641.35966558	545.35342044
264	1	0	88284	1263.81	1536.62	1776.43	724.85	636.2	909.49
265	1	0	88436	2899.88	852.36	2107.475542	1341.81	668.13	2093.9306793

Obs	_Imputation_	BRSTCAN	SWANID	DTTKCAL0	DTTKCAL5	DTTKCAL9	DTTPHOS0	DTTPHOS5	DTTPHOS9
266	1	0	88448	924.61	1344.86	1240.17	601.93	2039.52	1278.68
267	1	0	89112	2026.84	1503.44	1734.8492432	1455.87	1100.64	1530.9766655
268	1	0	89364	1949.93	1769.3792378	1791.862425	1182.44	705.18030108	1397.8367869
269	1	0	89467	1659.5	2023.79	1545.8	913.17	911.67	727.29
270	1	0	89456	1728.13	1578.31	2222.72	969.48	988.25	1849.96
271	1	0	89581	2030.21	2497.0734181	2340.1478982	1513.56	1663.2737413	1656.9968629
272	1	0	90243	1142.86	1186.94	1044.35	560.01	822.83	756.31
273	1	0	90794	1203.11	1602.06	1538.65	622.63	1191.34	1248.72
274	1	0	91574	2352.17	1718.88	2191.4862638	1237.55	1121.45	1481.4966613
275	1	0	91580	1145.11	1426.94	993.44	622.69	1045.33	864.55
276	1	0	91710	1470.06	874.11	1640.2681958	912.6	834.46559092	1492.5683472
277	1	0	92464	972.06	2737.18	2469.11	743.26	1669.58	1532.8
278	1	0	92723	1658.16	1863.14	1957.1823128	984.77	1097.66	1495.8949771
279	1	0	93492	1580.04	765.74	729.97	975.89	517.69	643.23
280	1	0	93615	1950.32	2088.79	1297.22	1580.05	1526.02	932.39
281	1	0	93727	1795.54	1408.57	1493.63	1724.26	1384.67	1219.73
282	1	0	93998	1449.93	1688.9055808	1028.1685707	887.44	962.84159241	435.57129977

Obs	_Imputation_	BRSTCAN	SWANID	DTTKCAL0	DTTKCAL5	DTTKCAL9	DTTPHOS0	DTTPHOS5	DTTPHOS9
283	1	0	94159	2170.49	1358.89	1351.95	937.11	1606.31	804.48
284	1	0	94589	1521.49	2304.22	2379.4604613	1037.26	1623.68	1459.81206
285	1	0	94937	1688.08	1498.57	1595.04	1225.99	778.18	1330.11
286	1	0	95398	1852.2	1647.9734133	774.27	1107.91	514.97888107	358.85
287	1	0	95756	1759.53	921.54	1394.93	835.83	711.23	941.57
288	1	0	95757	2117.3	2835.82	2155.1959152	1662.8	1470.85	1231.2658126
289	1	0	95760	1277.3	1590.06	1590.45	1222.95	1304.32	1700.95
290	1	0	96121	971.57	1130.4485595	1041.0421823	721.08	602.3292019	233.18874769
291	1	0	96187	4064.45	2742.7757581	2907.4860846	1741.02	1419.3542072	1806.4134699
292	1	0	96478	1352.06	1935.91	1483.21	1004.75	1273.42	994.07
293	1	0	97723	2651.46	809.67	2717.8	1608.95	833.5	1538.13
294	1	0	97995	2270.18	2378.0257461	2394.7120633	956.94	1235.6234451	1206.0126595
295	1	0	98030	1646.7	2266.248681	1811.59	1236.61	1510.3234374	1327.11
296	1	0	98106	1157.85	710.87	882.98	614.19	634.77	777.45

Appendix E

Mixed Effects Model Stepwise Recursive Procedure

Table 1

Model A: Random Intercept model.

$Y_{ij} = \beta_0 + \upsilon_{0i} + \varepsilon_{ij}$

Fit Statistics	
-2 Log Likelihood	-47921.9
AIC (Smaller is Better)	-47915.9
AICC (Smaller is Better)	-47915.9
BIC (Smaller is Better)	-47897.8

Solution for Fixed Effects					
Effect	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept	1.0472	0.003189	2212	328.42	<.0001

$\hat{y}_{ij} = 1.0472$

Table 2

Model B1: Fixed time trend model with Random intercept.

$Y_{ij} = \beta_0 + \beta_1 indiv\_visit_{ij} + \upsilon_{0i} + \varepsilon_{ij}$

Fit Statistics	
-2 Log Likelihood	-55250.4
AIC (Smaller is Better)	-55242.4
AICC (Smaller is Better)	-55242.4
BIC (Smaller is Better)	-55218.3

Solution for Fixed Effects					
Effect	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept	1.0841	0.003187	2212	340.16	<.0001
INDIV_VISIT	-0.00964	0.000099	15E3	-97.01	<.0001

$\hat{y}_{ij} = 1.0841 - 0.00964 indiv\_visit_{ij}$

Table 3

Model B2: Random intercept & trend model.

$Y_{ij} = \beta_0 + \beta_1 indiv\_visit_{ij} + \upsilon_{0i} + \upsilon_{1i} indiv\_visit_{ij} + \varepsilon_{ij}$

Fit Statistics	
-2 Log Likelihood	-60144.1
AIC (Smaller is Better)	-60132.1
AICC (Smaller is Better)	-60132.1
BIC (Smaller is Better)	-60095.9

Solution for Fixed Effects					
Effect	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept	1.0838	0.003106	2212	348.91	<.0001
INDIV_VISIT	-0.00939	0.000201	2121	-46.71	<.0001

$\hat{y}_{ij} = 1.0838 - 0.00939 indiv\_visit_{ij}$

Table 4

Model C: Effect of BRSTCAN on intercept and trend.

$Y_{ij} = \beta_0 + \beta_1 indiv\_visit_{ij} + \beta_2 brstcan_i + \upsilon_{0i} + \upsilon_{1i} indiv\_visit_{ij} + \varepsilon_{ij}$

Fit Statistics	
-2 Log Likelihood	-60144.2
AIC (Smaller is Better)	-60130.2
AICC (Smaller is Better)	-60130.2
BIC (Smaller is Better)	-60087.9

Solution for Fixed Effects						
Effect	**Breast Cancer RUN**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept		1.0838	0.003106	2212	348.91	<.0001
INDIV_VISIT		-0.00939	0.000201	2121	-46.71	<.0001
BRSTCAN	Yes	0.000881	0.003661	13E3	0.24	0.8098
BRSTCAN	No [Ref]	0	.	.	.	.

$\hat{y}_{ij} = 1.0838 - 0.00939 indiv\_visit_{ij} + 0.000881 brstcan_i$

AICC is smaller than model B2. BRSTCAN is not significant.

Table 5

Model D: Effect of BRSTCAN*INDIV_VISIT on intercept and trend.

$$У_{ij} = \beta_0 + \beta_1 indiv\_visit_{ij} + \beta_2 brstcan_i + \beta_3(indiv\_visit_{ij} * brstcan_i) + \upsilon_{0i} + \upsilon_{1i} indiv\_visit_{ij} + \upsilon_{ij}$$

Fit Statistics	
-2 Log Likelihood	-60154.1
AIC (Smaller is Better)	-60138.1
AICC (Smaller is Better)	-60138.1
BIC (Smaller is Better)	-60089.8

Solution for Fixed Effects						
Effect	**Breast Cancer RUN**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept		1.0837	0.003106	2212	348.88	<.0001
INDIV_VISIT		-0.00937	0.000201	2121	-46.58	<.0001
BRSTCAN	Yes	0.02130	0.007439	13E3	2.86	0.0042
BRSTCAN	No [Ref]	0	.	.	.	.
INDIV_VISIT*BRSTCAN	Yes	-0.00411	0.001302	13E3	-3.15	0.0016
INDIV_VISIT*BRSTCAN	No [Ref]	0	.	.	.	.

$$\hat{y}_{ij} = 1.0837 - 0.00937 indiv\_visit_{ij} + 0.02130 brstcan_i - 0.00411(indiv\_visit_{ij} * brstcan_i).$$

BRSTCAN is significant at 0.0042, and the interaction INDIV_VISIT*BRSTCAN is significant at 0.0016.