

CONTRALATERAL BREAST CANCER

M.Sc. Thesis- Punam Rana; McMaster University- Clinical Epidemiology and Biostatistics

CONTRALATERAL BREAST CANCER IN WOMEN WITH EARLY STAGE BREAST CANCER

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A Thesis Submitted to the School of Graduate Studies in Partial Fulfilment of the
Rquirements for the Degree Master of Science

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LAY ABSTRACT

The rate of contralateral breast cancer in women with early stage breast cancer is uncertain. In order to determine this rate, a systematic review and meta analysis was conducted. The rate of contralateral breast cancer in women with early stage breast cancer was found to be 0.36% per year. This rate appears to be constant for up to 10 years after the original breast cancer diagnosis. This data is important for women with breast cancer and their healthcare teams in order to make decisions about bilateral mastectomy.

ABSTRACT

Background:

There is uncertainty about the lifetime risk of contralateral breast cancer (CBC) in a woman who is diagnosed with early stage breast cancer. Studies report a wide range of rates of CBC between 2% and 35%.

Objectives:

(i) To determine the risk of CBC in women with early stage breast cancer, and (ii) to evaluate the risk of CBC in women who undergo adjuvant systemic treatment and adjuvant radiation treatment.

Methods:

PubMed, Ovid MEDLINE, EMBASE, Healthstar, Cochrane Central Register for Controlled Trials were searched. Studies were included if participants had: unilateral invasive breast carcinoma; 5 years of median follow-up; a minimum of 100 participants. Randomized controlled trials were included for the meta-analysis. A random-effects meta-analysis was used to estimate the pooled rate of CBC.

Results:

4571 articles were extracted out of which 22 randomized controlled trials were included in the final meta-analysis. The overall pooled rate of CBC was 0.36% per year, (95% CI, 0.32% - 0.41%). The rate of CBC in studies without adjuvant systemic treatment was higher than the rate without such treatment, 0.56% per year (95% CI, 0.40% to 0.77%) versus 0.35% per year (95% CI, 0.31% to 0.40%). The rate of CBC in studies with adjuvant radiation treatment was 0.26% per year (95% CI, 0.18% to 0.39%) which is similar to the rate in studies with radiation.

Conclusions:

The rate of CBC in women with early stage breast cancer is relatively low. This is important for breast cancer patients who are considering contralateral prophylactic mastectomy.

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LIST OF ABBREVIATIONS

CPM	Contralateral Prophylactic Mastectomy
CBC	Contralateral Breast Cancer
RCT	Randomized Controlled Trial
SEER	Surveillance, Epidemiology, End Results

DECLARATION OF ACADEMIC ACHIEVEMENT

This thesis contains no material that has been accepted for the award of any other degree of diploma in any educational institution. To the best of my knowledge, it contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

Chapter 1: Introduction

1.1 Background

Breast cancer is the most common cancer for women worldwide. It is estimated that 24,400 Canadian women were diagnosed with breast cancer in 2014, representing 26% of all new female cancer cases in Canada (Canadian Cancer Statistics 2014). Five thousand Canadian women are expected to die from breast cancer, representing 14% of all female cancer deaths in Canada. A majority of women diagnosed with breast cancer present with stages I or II where the cancer is relatively small i.e. < 5 cm and is confined to the breast tissue or local lymph nodes (American Cancer Society 2012). Stage I and II are often referred to as early stage breast cancer and constitute about 75% of breast cancers. Women with stage I or II breast cancer are most often treated with surgery followed by radiation therapy and systemic therapy e.g. chemotherapy and /or endocrine therapy to prevent recurrence. Stage III breast cancer, which makes up about 10-15% of cases, connotes large bulky tumor in the breast and /or axillary lymph nodes and is considered to be locally advanced disease. Patients with Stage III disease are usually treated with an aggressive multi-disciplinary approach consisting of chemotherapy followed by surgery and radiation. Five to ten percent of women with breast cancer present with stage IV disease which indicates that it has spread outside of the breast and lymph nodes. Stage IV breast cancer is typically managed with long-term systemic therapy rather than an aggressive curative approach. The 5-year survival rates for patients who present with stage localized (lymph node negative), regional (lymph

node positive), and distant (stage IV) disease are 99%, 84%, and 24% respectively (American Cancer Society, 2013) as per the SEER database.

Women who present with early stage breast cancer are initially referred to a surgeon for surgical removal of the tumor in addition to assessment of the axillary lymph nodes for breast cancer cells. Two surgical options are available which are equally efficacious in treating early stage breast cancer. A mastectomy involves surgical removal of all breast tissue whereas a lumpectomy involves surgical excision of the tumor. The latter approach is followed by local radiation to reduce the rate of breast cancer recurrence in the remaining breast tissue. The decision to undergo a lumpectomy versus mastectomy depends on practical aspects of the tumor including size and mobility, suitability for radiation, as well as patient preference. A mastectomy may allow a patient to avoid radiation therapy whereas a lumpectomy offers an opportunity to minimize surgical invasiveness and preserve remaining breast tissue. Both surgical approaches are considered to be equally efficacious with equivalent survival rates.

Post-operatively a patient with early stage breast cancer is referred to a medical oncologist for consideration of adjuvant systemic therapy. Adjuvant therapy refers to treatment given in conjunction to the primary treatment modality, namely surgery. Adjuvant therapy is administered to treat potentially occult micro-metastases which may be present in the breast tissue, the lymph nodes, distant tissues or may be circulating in the blood and pose risk for breast cancer recurrence either locally or distally. A patient's risk of micro-metastasis depends on breast

cancer factors including tumor size, grade, lymph node involvement, and hormone receptor status. Patients at high risk are usually offered chemotherapy to reduce the relative risk of recurrence by 20-40% and improve the relative overall survival by 10-20% (Early Breast Cancer Trialists' Collaborative Group, 2012). In addition to chemotherapy, patients with estrogen receptor positive breast cancer are offered 5 to 10 years of treatment of endocrine therapy with either tamoxifen or an aromatase inhibitor in order to reduce the relative risk of recurrence by 45% and mortality by 30% (Early Breast Cancer Trialists' Collaborative Group 2012).

Early stage breast cancer patients are also assessed by a radiation oncologist for consideration of adjuvant radiation to the breast and lymph nodes. Over one half of women with early stage breast cancer undergo a lumpectomy (Kurian, 2014) and are therefore candidates for adjuvant radiation. For women who undergo a mastectomy, the radiation oncologist reviews the risk of micro-metastasis in the breast tissue or lymph nodes and recommends adjuvant radiation to those who are at high risk.

Patients who present with locally advanced breast cancer are also assessed by the surgical, medical, and radiation oncologists and typically receive chemotherapy prior to surgery. This preoperative, or neo-adjuvant, chemotherapy approach allows more women to undergo lumpectomy rather than mastectomy. However patients who present with truly locally advanced Stage III breast cancer which is initially inoperable but rendered operable with chemotherapy undergo a

mastectomy. Locally advanced breast cancer patients receive radiation post-operatively.

Women with early stage or locally advanced breast cancer are closely monitored for the subsequent five years. Current American Society of Clinical Oncology (ASCO) guidelines recommend that each breast cancer patient undergo a physical examination every 4 to 6 months for the first two years and annually thereafter until year 5. An annual mammogram should be performed because of an increased risk of ipsilateral breast cancer (Khatcheressian, 2013). Ipsilateral refers to the side in which the original breast cancer presented and applies to women who have undergone lumpectomy. Approximately 5% of women with early stage breast cancer will experience a recurrence in the ipsilateral breast within 5 years of follow-up (Whelan, 2011). Contralateral, on the other hand, refers to the breast opposite to the original breast cancer. The risk of contralateral breast cancer is less certain, unless there is a known genetic mutation.

Approximately 5% of women with breast cancer have a BRCA genetic mutation and are at high risk of breast cancer recurrence in both the ipsilateral and contralateral breast cancer. In a retrospective review of over 2000 patients with family history of a BRCA1 or BRCA2 mutation, the cumulative risk for contralateral breast cancer 25 years after first breast cancer was 47.4% (95% CI, 38.8% to 56.0%) (Graeser, 2009). It is recommended that patients with a known genetic mutation undergo preventative mastectomy on the contralateral breast, known as a contralateral prophylactic mastectomy (ESMO Guidelines Working Group, 2010).

For women who do not have a genetic predisposition, however, this procedure is not recommended because the benefits are less clear.

Although it is not routinely recommended for breast cancer patients who do not have a genetic mutation, the rate of contralateral prophylactic mastectomy for patients with early stage breast cancer is on the rise. According to the surveillance, epidemiology, and end results (SEER) program data, the rate of contralateral prophylactic mastectomy increased from 4.2% in 1998 to 11% in 2003 (Tuttle, 2009). More recent data suggests that rates have continued to increase up to 14% (King, 2011). Increased rates of contralateral prophylactic mastectomy have also been detected by the American National Cancer Data Base (NCDB) as well as in single institution studies (Tracy, 2013).

Women who are more likely to undergo contralateral breast cancer are: younger in age; married; more educated; have a higher socio-economic status; more likely to be non-Hispanic whites; and have a family history of breast or ovarian cancer. Tumor characteristics which have been found to be associated with undergoing a contralateral prophylactic mastectomy are: larger size; lower grade; lobular subtype; lymph node negativity (Kurian, 2014).

The etiology for this increase is multi-factorial including a desire to reduce anxiety about a second breast cancer (Murphy, 2013), diminished need for surveillance, cosmetic symmetry and decreased risk of contralateral breast cancer (Tracy, 2013). Up to 95% of women in the Young Women's Breast Cancer Study state that peace of mind was also a very important benefit of contralateral

prophylactic mastectomy (Helwick, 2015). Contralateral mastectomy is associated with a 90-97% risk reduction of contralateral breast cancer (Herrinton, 2005). Contralateral prophylactic mastectomy (CPM) may be more cost-effective than regular surveillance among women under the age of 70 (Zendejas, 2011) and there may be reduced health care costs by preventing treatment of a new contralateral breast cancer (Murphy, 2013). Generally, satisfaction with contralateral prophylactic mastectomy is high among women who have it (Geiger, 2006; Montgomery, 1999).

A contralateral prophylactic mastectomy is not without risks including those inherent to surgical operations and post-operative settings and a risk of requiring follow up procedures. A retrospective review which included 4219 patients who underwent sentinel lymph node biopsy compared those who underwent a unilateral mastectomy (3,722) versus a bilateral mastectomy (497). The overall 30-day complication rate was almost doubled for those who underwent bilateral mastectomy: 7.6% versus 4.2% (OR=1.9, P<.05) (Osman, 2013). In addition, booking patients for contralateral prophylactic mastectomy leads to increased use of valuable operating time which may be limited.

A retrospective review found that that women who undergo contralateral prophylactic mastectomy are at high risk of depression (Tuli, 2010). In an observational questionnaire-based study of 296 patients who underwent contralateral prophylactic mastectomy, 6% expressed regret for completing the procedure due to: poor cosmetic results (39%), diminished sense of sexuality (22%)

and lack of education regarding alternative surveillance methods (22%)

(Montgomery, 1999).

It is reported that patients who opt for a contralateral prophylactic mastectomy tend to overestimate their risk of contralateral breast cancer especially compared to the risks associated with the index cancer (Davies, 2015). However there is no clear consensus about the risk of contralateral breast cancer. Different studies have quoted vastly differing estimates of the lifetime risk of contralateral breast cancer from 3.5% (Adami, 1985) to greater than 30% (Storm, 1986), with most studies reporting rates somewhere in between. This poses a clinical dilemma for women with early stage breast cancer who will, in part, base their decision about contralateral prophylactic mastectomy on the underlying risk of contralateral breast cancer. It is therefore important to determine the risk of contralateral breast cancer in women with early stage breast cancer, who do not have a genetic mutation, in order to facilitate informed decisions regarding contralateral prophylactic mastectomy. The present study will include a systematic review and meta-analysis of the medical literature to determine the lifetime risk of contralateral breast cancer in women with early stage breast cancer.

1.2 Statement of the Problem

There is uncertainty about the lifetime risk of contralateral breast cancer in a woman who is diagnosed with early stage breast cancer. It is important to establish

this risk so that women with early stage breast cancer can make informed decisions about contralateral prophylactic mastectomy.

1.3 Purpose of the Study

The purpose of this study is to establish the best estimate of the risk of contralateral breast cancer in women who present with early stage breast cancer. This study will include all women with early stage breast cancer from a global perspective i.e. using data from countries around the world where this data is available. Studies which only include women with genetic mutations associated with breast cancer will be excluded.

1.4 Significance of the Study

The results of this study will inform both health care practitioners and early stage breast cancer patients about the risk of contralateral breast cancer. This study will provide the most up-to-date and accurate estimate of this risk. This will also help facilitate agreement amongst the various physicians involved with the care of a breast cancer patient, including the surgical, radiation, and medical oncologist, ensuring that the patient receives a consistent risk estimate.

Chapter 2: Research Design and Methods

2.1 Overview

A literature review is a method used to summarize relevant evidence and can be particularly useful in helping to answer a clinical question (Guyatt, 2008). A narrative review is a type of review traditionally used in medical textbooks. It does not necessarily involve a comprehensive review of the literature. A systematic review, alternatively, answers a specific clinical question in a systematic and reproducible manner. A systematic review may include a quantitative synthesis of the data, referred to as a meta-analysis, although this is not mandatory. The differences between a narrative review and a systematic review have been previously published (Cook, 1997):

Characteristic	Narrative Review	Systematic Review
Clinical Question	Seldom reported, or addresses several general questions	Focused question specifying population, intervention, or exposure and outcome
Search for primary articles	Seldom reported; if reported, not comprehensive	Comprehensive search of several evidence sources
Search of primary articles	Seldom reported; if reported, often biased sample of studies	Explicit inclusion and exclusion criteria for primary studies
Evaluation of quality of primary articles	Seldom reported; if reported, not usually systematic	Methodological quality of primary articles is assessed
Summary of results of primary studies	Usually qualitative nonsystematic summary	Synthesis is systematic (qualitative or quantitative; if quantitative, this is often referred to as meta-analysis)

In my thesis, a systematic review and meta-analysis will be conducted. A systematic review is useful when a single clinical trial is insufficient to answer a clinical question. There are often discrepancies seen in the results between a single

clinical trial and the pooled results of multiple trials (Cappelleri, 1996; LeLorier, 1997). One advantage to a systematic review compared to a single trial is that inclusion of multiple studies allows for a broader patient population and settings which in turn increases the generalizability of results. In addition, combining the results of multiple studies increases the sample size and may produce a more precise estimate of the effect size compared to a single study. A systematic review is particularly helpful for healthcare providers who may not have the time or resources to critically evaluate all of the body of evidence to answer a clinical question.

The process of conducting a systematic review (Guyatt, 2008) begins with defining the question. The question should specify the eligibility criteria for studies which will be included in the review including: the population, the exposures, outcomes of interest, and the methodology of the studies to be included. Once the question is specified, the information sources from which to extract the data need to be specified. After the reviewer conducts the initial search, titles and abstracts which may potentially meet inclusion criteria are identified. Inclusion and exclusion criteria are applied to these abstracts in order to select articles which will be reviewed in full. The final articles are then reviewed in detail and data are abstracted. Each article is also assessed for methodological rigor. When a meta-analysis is also conducted with the systematic review, the estimates across the studies are pooled. Details about the statistical approach are provided in subsequent sections of this chapter.

2.2 Defining the Question

The question in a systematic review must not be too broad or too narrow. The underlying biology should ideally elicit the same treatment effect across the included range of patients. The following questions proposed by Guyatt et al (Guyatt, 2008) are helpful in directing the scope of the question for a systematic review (Guyatt, 2008): Are results likely to be similar across the range of patients included (e.g. older and younger, sicker and less sick)? Are results likely to be similar across the range of ways the outcome was measured (e.g. shorter or longer follow-up)? This emphasis on finding the right scope is to ensure that the question being asked is one which would allow for generalizability to a clinical scenario and would be clinically relevant.

The following question will be answered in this systemic review: *In women with early stage invasive breast cancer, what is the risk of a contralateral and metachronous breast cancer?*

2.2.1 Inclusion and Exclusion Criteria

Inclusion and exclusion criteria for this meta analysis are listed in the following table:

Inclusion Criteria
Population - Women with early stage invasive breast cancer
Outcome - Contralateral breast cancer

- Metachronous breast cancer (ie diagnosed >6 months after primary breast cancer)
Methodology <ul style="list-style-type: none"> - Randomized controlled trials - Studies that include >=100 subjects
Exclusion Criteria
Population <ul style="list-style-type: none"> - Women with DCIS or LCIS only - Women with an increased risk of breast cancer (genetic mutation, family history)
Outcome <ul style="list-style-type: none"> - Ipsilateral breast cancer - Synchronous contralateral breast cancer (diagnosed <6 months after primary breast cancer)
Methodology <ul style="list-style-type: none"> - Cohort studies - Case control studies - Studies which include <100 subjects

Studies are eligible for inclusion if the participants are women with invasive carcinoma of the breast including all subtypes (ductal, lobular, and other rare subtypes). Studies which exclusively include women diagnosed with ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS) are not eligible because these precancerous breast lesions have different patterns for risk of recurrence compared to invasive carcinoma and for risk of contralateral breast cancer (CBC). Inclusion of studies of only patients with DCIS or LCIS could result in a selection bias and could affect the results. Studies which include both women with invasive breast cancer and DCIS are also to be excluded for the same reason. In addition, studies which include a specific subpopulation of breast cancer patients are ineligible for inclusion because of selection bias and therefore reduced generalizability. For

example, studies which include only patients with a genetic mutation, a family history, or with multiple breast cancers will be excluded

Studies that are eligible for inclusion must report contralateral breast cancer (invasive breast cancer diagnosed in the opposite breast of the primary cancer) and metachronous breast cancer (invasive breast cancer which is diagnosed at least 6 months after the primary breast cancer diagnosis). Synchronous contralateral cancers diagnosed less than 6 months after the primary diagnosis are excluded from the analysis because they are biologically different from metachronous cancers and confer a worse prognosis (Kollias, 2001).

This meta analysis will include randomized controlled trials (RCTs) only. The justification for this criteria is provided in Chapter 3: Critical Appraisal.

2.3 Literature Search

The search engines which will be used are PubMed, Ovid MEDLINE, EMBASE, Healthstar, and Cochrane Central Register for Controlled Trials. The search strategy employed in each search engine was based on guidelines from the Cochrane Handbook for Systematic Reviews of Interventions (Higgins, 2011) and is tailored to the specific search structure of each engine. The following section will provide some background information on each search engine and will display the specific search strategy utilized for that database.

2.3.1 MEDLINE

MEDLINE is the U.S. National Library of Medicine premier bibliographic database which contains over 21 million references from over 5,600 worldwide journals from the 1946 onwards. The majority of publications are scholarly journals. A majority of journals are selected for MEDLINE based on recommendation of the Literature Selection Technical Review Committee of the National Institute of Health. The subject scope of MEDLINE is health and biomedicine and the target audience is health professionals and others engaged in basic research and clinical care, public health, or health policy development (MEDLINE Fact Sheet [online]).

MEDLINE Search Strategy:

- | | |
|----|--|
| 1 | Breast Neoplasms/ (218820) |
| 2 | (breast adj6 cancer\$.mp. (182232) |
| 3 | (breast adj6 neoplasm\$.mp. (221217) |
| 4 | (breast adj6 carcinoma\$.mp. (54701) |
| 5 | (breast adj6 tumour\$.mp. (6088) |
| 6 | (breast adj6 tumor\$.mp. (28196) |
| 7 | exp Neoplasms, Second Primary/ (10512) |
| 8 | 1 or 2 or 3 or 4 or 5 or 6 or 7 (273495) |
| 9 | contralateral.mp. (64115) |
| 10 | contralateral*.mp. (65349) |
| 11 | 9 or 10 (65349) |
| 12 | 8 and 11 (2563) |

2.3.2 PubMed

PubMed is a free resource developed and maintained by the National Center for Biotechnology Information (NCBI) at the National Library of Medicine. A unique feature of PubMed is the ability to instantly find related articles for any citation.

PubMed may contain many of the publications included in MEDLINE, but also

contains articles related to general science and chemistry and books and book chapters available on the NCBI Bookshelf.

PubMed Search Strategy:

- | |
|---|
| 1. "Search (((breast neoplasms) OR ("breast" AND "neoplasms")) OR ("breast" AND "cancer")) OR breast cancer" (293129) |
| 2 "Search ((contralateral) OR "contralateral") OR contralateral*" (69522) |
| 3 "Search (#1 AND #2)" (2659) |

2.3.4 EMBASE

EMBASE is a database published by Elsevier which contains over 28 million records from over 8400 published journals dating back to 1947 including over 6 million records that are not covered by MEDLINE. However, MEDLINE also publishes articles which are not found in EMBASE (Higgins, 2011). EMBASE also has extensive conference abstract coverage and covers over 1000 conferences annually (EMBASE online).

EMBASE Search Strategy:

- | |
|---|
| 1 breast cancer.mp. or breast cancer/ (320645) |
| 2 breast carcinoma.mp. or breast carcinoma/ (59339) |
| 3 (breast adj6 cancer\$.mp. (359109) |
| 4 (breast adj6 neoplasm\$.mp. (28457) |
| 5 (breast adj6 carcinoma\$.mp. (77660) |
| 6 (breast adj6 tumour\$.mp. (8594) |
| 7 (breast adj6 tumor\$.mp. (120278) |
| 8 second cancer.mp. or second cancer/ (8490) |
| 9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (420564) |
| 10 contralateral.mp. (76972) |
| 11 contralateral*.mp. (78335) |
| 12 10 or 11 (78335) |
| 13 9 and 12 (3920) |

2.3.5 CENTRAL (Cochrane)

The Cochrane Central Register of Controlled Trials (CENTRAL) is a comprehensive source of publications of controlled trials. CENTRAL is published as part of *The Cochrane Library* (Higgins, 2011). CENTRAL contains over 530,000 citations of which approximately half are obtained from MEDLINE and EMBASE. The remaining citations are obtained from other databases and hand-searching and other sources which are otherwise difficult to access (Dickersin, 2002). It also includes records from trials registers and trials results registers.

CENTRAL Search Strategy:

- | |
|--|
| 1 MeSH descriptor: [Breast Neoplasma] explode all tress (8904) |
| 2 breast near cancer* (18166) |
| 3 breast near neoplasm* (9427) |
| 4 breast near carcinoma* (1714) |
| 5 breast near tumour* (403) |
| 6 breast near tumor* (938) |
| 7 #1 or #2 or #3 or #4 or #5 or #6 (19684) |
| 8 contralateral* (3407) |
| 9 #7 and #8 (270) |
| 10 limited to "trials" and "other reviews" (216) |

2.3.6 Healthstar

Healthstar is a database used to identify publications which deal with clinical and non-clinical aspects of health-care delivery obtained from MEDLINE, the Hospital Literature Index, and other selected journals. Healthstar encompasses

citations related to administration, effectiveness of health services, and health economics (How to use HealthStar [online]).

Healthstar Search Strategy:

1	exp Breast Neoplasms/ (212700)
2	(breast adj6 cancer\$.mp. (165891)
3	(breast adj6 neoplasm\$.mp. (212869)
4	(breast adj6 carcinoma\$.mp. (48849)
5	(breast adj6 tumour\$.mp. (5468)
6	(breast adj6 tumor\$.mp. (23946)
7	exp Neoplasms, Second Primary/ (7840)
8	1 or 2 or 3 or 4 or 5 or 6 or 7 (243779)
9	contralateral.mp. (27515)
10	contralateral*.mp. (27897)
11	9 or 10 (27897)
12	8 and 11 (2555)

2.3.7 Screening for Relevant Articles

Screening for articles which fit the inclusion criteria is a multi-step process which involves an initial title screening followed by abstract screening and finally, by full-text screening using a Full Text Screening Form. RefWorks (Refworks [online]) is a bibliographic database management program which supports hundreds of online databases and output styles which was used to track and organize articles obtained from all of the searches, as well as those included at each stage of review (title screening, abstract screening, full-text screening).

2.4 Data Extraction

2.4.1 Log Transformation

Transformation is a method which can be used in data analysis when a variable is replaced by a function of that variable. For example, a rate could be converted to the logarithm of the rate which is called a log transformation. A transformation may be useful for several reasons including convenience (Cox, 2015). A transformed scale may be more convenient for a specific purpose such as using percentages rather than original data (Keene, 1995). Additional advantages to using a logarithmic transformation include focus of the analysis on clinically more appropriate measures of effect, changing the shape of a distribution, and dealing with skewed outcome data.

In this analysis, a log transformation has been implemented for convenience purposes. Normally, an analyses of rate assumes the Poisson distribution. The Poisson distribution expresses the probability of a given number of events occurring in a fixed interval of time which occur with an average rate (Haight, 1967). Given the assumption of the Poisson distribution, the variance of the calculated rate is equal to the rate, which poses challenges for calculating the weight of each study which is equal to $1/\text{rate}$ and therefore $1/\text{variance}$. By implementing the log transformation, the variance is equal to 1 divided by the number of events and the analysis is therefore more convenient.

2.4.1 Estimating the Rates

The rate of contralateral breast cancer was calculated by using the following formula:

$$\text{Rate} = \frac{\text{Events}}{\# \text{ Participants} \times \text{Median Follow-up}}$$

which yields the rate per person time. As per this equation, the data points extracted from each article were: the number of contralateral breast cancer events which occurred in the study; the total number of study participants; the median follow-up time of all participants. The calculated rate was then converted using a log transformation into a log rate. This assumes that the rate is constant across all follow-up time points, known as the exponential distribution, which is appropriate for the Poisson distribution.

2.5 Assessing for Heterogeneity

A meta-analysis is a useful method to combine results from different studies to arrive at a conclusion about a body of research (Rothman, 2008). Ideally, when combining the results of different studies, they would each have similar methods and design. However, in biomedical studies, the assumption of homogeneity in meta-analysis can seldom be made (Higgins, 2009). Variability between studies can be evaluated visually by using a forest plot and statistically by using two techniques: the Q test, and the I^2 statistic. If there is no evidence of heterogeneity, then a fixed effects model may be used which assumes that all the included studies share a common effect size and that the observed effects will be distributed around μ , with a variance which depends primarily on the sample size of the study. Alternatively, if the results of these tests suggest that the studies have significant heterogeneity, then a random-effects model must be employed when combining results. The random

effects model assumes that the true effect size, μ , varies in each study and that the meta-analysis represents a random sample of effect sizes that could be observed. The final summary effect is the estimate of the mean of these effects (Borenstein, 2009).

2.5.1 The Forest Plot

The forest plot displays the effect size of all included studies in a meta-analysis and provides a visual estimation of the variation between the studies. Effect size is plotted on the x axis and included studies are listed on the y axis. A horizontal line runs through each effect size representing the 95% confidence interval. An outlier study must be examined more closely to look for possible differences in study design, intervention, or patient population, which render it unique from the other studies. Significant heterogeneity in a study may warrant removal of that study from the analysis.

2.5.2 The Q Test

The Q test measures heterogeneity among studies. The Q test is distributed as a chi-square statistic with $k-1$ degrees of freedom, where k represents the number of studies. A low P value (or a large chi-squared statistic relative to its degrees of freedom) is evidence for heterogeneity and suggests variation in effect estimates beyond chance.

The formula for the Q test, proposed by Cochran (Cochran, 1954) and defined by Hedges & Olkin (Hedges, 1985):

$$Q = \sum w_i (T_i - \bar{T})^2$$

where W_i is the weight of study, i , and T_i is the effect size of study, i . T equals the sum of the weight x rate divided by the sum of all weights. One drawback of the Q test is that it tends to have low power against the alternative and therefore acceptance of the null hypothesis should not be taken as firm evidence that there is no study variation in outcomes (Laird, 1990).

2.5.3 The I^2 statistic

Whereas the Q test is used to either accept or reject the null hypothesis that the studies are all similar, the I^2 statistic is used to quantify heterogeneity amongst studies in a meta-analysis. Proposed by Higgins and Thompson (Higgins, 2002), the I^2 statistic quantifies the extent of heterogeneity from a collection of effect sizes by comparing the Q value to its expected value assuming homogeneity. It is expressed as a percentage of the total variability in a set of effect sizes due to between-study variability. The formula for I^2 is:

$$I^2 = \frac{Q - (k - 1)}{Q} \times 100\%$$

where Q is the chi-squared statistic and $(k-1)$ refers to the degrees of freedom. This describes the percentage of the variability in effect estimates that is due to the heterogeneity rather than sampling error. The following table from the Cochrane Handbook (Higgins, 2011) provides a guideline for interpreting the I^2 statistic:

Interpretation of I ² Statistic for Heterogeneity	
0% to 40%	Might not be important
30% to 60%	May represent moderate heterogeneity
50% to 90%	May represent substantial heterogeneity
75% to 100%	Considerable heterogeneity

Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0

2.6 The Random Effects Model

A random effects model is used when it cannot be assumed that the studies in the meta-analysis have the same effect size as one another. Of note, in a meta-analysis where the sample populations are thought to be significantly different from one another, a random effects model may be used despite the results of the Q test and I² statistic (Neyeloff, 2012). In this meta-analysis where the studies are comprised of a variable set of patient populations and interventions, the fixed effects model would be considered most appropriate despite the results the Q test and I² statistic.

A common random-effects meta-analysis approach is known as the DerSimonian and Laird method (DerSimonian, 1986). In this approach, the standard errors of the study-specific estimates are adjusted to incorporate a measure of the extent of variation, or heterogeneity, among the effect sizes observed in different studies. The amount of variation, and therefore adjustment, is estimated from the effect sizes and standard errors of the studies included in the meta-analysis (Higgins, 2011).

Using the DerSimonian random-effects model, the weighted mean rate is calculated using the following formula:

$$\bar{X}_w = \frac{\sum W_i X_i}{\sum W_i}$$

where W_i is the weight of study, i , and X_i is the rate of study, i . The weight of the study in a random effects model is inverse to the sum of the within study variance and between study variance. It is calculated with the following formula:

$$W_{iRE} = \frac{1}{V_i + V_\theta}$$

where V_i is the between study variation and V_θ is the variance for each study. The variance between studies is equal to:

$$V_i = \frac{Q - df}{\sum w_i - \frac{\sum w_i^2}{\sum w_i}}$$

where Q is equal to the Q statistic (see section 5.1.2) and the df is equal to the degrees of freedom. The variance for each study is calculated using the following formula:

$$V_\theta = \frac{1}{Events}$$

The variance for the weighted mean is calculated with the following formula:

$$v_{\cdot}^* = \frac{1}{\sum_{i=1}^k w_i^*}$$

and the standard error is calculated as:

$$SE(\bar{T}_{\cdot}^*) = \sqrt{v_{\cdot}^*}$$

$$\text{Lower Limit}^* = \bar{T}_{\cdot}^* - 1.96 * SE(\bar{T}_{\cdot}^*)$$

$$\text{Upper Limit}^* = \bar{T}_{\cdot}^* + 1.96 * SE(\bar{T}_{\cdot}^*)$$

Chapter 3: Critical Appraisal

3.1 Evaluating Disease Prognosis

Determining the rate of contralateral breast cancer in women with early stage breast cancer is a question which relates to disease prognosis, i.e. the probability of an outcome developing in the natural history of an illness (Department of Clinical Epidemiology and Biostatistics, MUHSC). Different study designs may be used to address questions regarding disease prognosis. The types of studies used for prognosis are: randomized controlled trials (RCTs), observational studies including prospective and retrospective cohort studies, and population-based registries.

In an RCT there is a random assignment of patients to a treatment arm in order to minimize differences in patient characteristics between the arms which may lead to inaccurate results due to confounding variables. The randomization process strengthens the internal validity of an RCT, which is considered to be of the highest quality of evidence (Guyatt, 2011). Follow-up of RCTs is prospective and patients adhere to a specific follow-up plan. Typically RCTs are used to compare two or more interventions, but in an analysis of disease prognosis the arms of the RCT can be considered as prospective cohorts. Disadvantages to RCTs include that they have limited external validity and they can be very resource intensive, being both costly and time-consuming.

A prospective cohort study is one in which the investigator defines the sample of subjects, measures factors that can be associated with outcomes and

follows the subjects for outcomes. This design can be useful for assessing incidence particularly for relatively common diseases. A prospective cohort study is considered to be of superior quality to a retrospective cohort study in which assembly of the cohort, baseline measurements, and follow-up have occurred in the past. Data obtained from retrospective studies may be incomplete, inaccurate, or measured in ways that are not ideal for answering the question at hand (Hully, 2007). A disadvantage of both prospective and retrospective cohort studies compared to RCTs is that results are more likely to be biased due to confounding variables, factors which themselves can influence prognosis. In addition, while RCTs tend to follow patients regularly according to a predefined protocol, the follow-up of patients in observational studies may be irregular and therefore studies of this design may capture fewer outcomes than RCTs (Hannan, 2008).

Case control studies are an example of observational studies which are not used for prognostic evaluation. Case control studies identify and compare subjects who have an outcome of interest to those who do not. The two groups are then retrospectively examined for potential associated variables. These studies are not useful for studying prognosis because the proportion of study subjects with the outcome is not related to the proportion in the population, but rather is predetermined by the investigator.

Finally, population-based registries, which are considered to be secondary data sets, can be used to study prognosis. Cancer registries are either government-supported agencies or hospital-based databases that collect, classify, and consolidate

information about cancer incidence and mortality from various resources including hospital reports, medical records, and death certificates (Dos Santos, 2015). Cancer registries are helpful to monitor regional cancer patterns. However there are several issues which may affect the quality of the information obtained from a cancer registry including missing data, delayed data reporting, repeat reports per patient, and misclassifications (Izquierdo, 2009). Confounding is another source of bias which is also present in population based registries.

RCTs, observational studies, and population registries can all be useful in evaluating disease prognosis and each approach has advantages and disadvantages. RCTs are considered to be of highest quality of evidence as they are the least likely to be biased. They are also the most likely to report the outcome of interest, in this case the occurrence of contralateral breast cancer, as they provide a clear inception cohort and have the most rigorous follow-up approach. It is for these reasons, and in the interest of efficiency and resources for completing my thesis, that this meta-analysis will focus solely on RCTs.

The following table summarizes the 22 RCTs which will meet the eligibility criteria for this study (Table 1).

Table 1: Summary of Included Studies

Study	Patient Population	No of Subjects	Median follow-up (years)	Arms	
				Control	Treatment
ATAC 2008	Postmenopausal women with localized invasive cancer who completed	6241	8.3	Tamoxifen x 5 years	Anastrozole x 5 years

	primary surgery +/- chemo and were candidates to receive adjuvant hormonal therapy				
SBCCG 1996	Postmenopausal women under the age of 75 years with operable, axillary lymph node-negative or -positive, invasive breast cancer	3545	5.0	Tamoxifen x 2 years	Tamoxifen x 5 years
GIVO 1994	Women <70y with operable (T1 to T3, N0 to N1, or M0) noninflammatory, unilateral breast carcinoma	1320	5.9	Usual follow-up	Intensive Surveillance
Alkner 2009	Unifocal, stage II invasive breast cancer who received surgery with axillary node dissection +/- radiotherapy, +/- polychemotherapy	564	14.0	No Tamoxifen	Tamoxifen x 2 years
Arriagata 1996	All patients <70y with unilateral breast tumor classified as T1a, N0, N1a, or Nb, M0	179	14.5	Mastectomy	Lumpectomy + Radiation
Arriagata 2002	Women with primary infiltrating ductal or lobular breast carcinoma with one of: positive lymph nodes or Grade II or III, who had last menses > 1 year prior to diagnosis	835	5.0	Tamoxifen x 2 years	Chemotherapy (FAC or FEC) followed by tamoxifen x 2 years
Chlebowski 2006	Women with resected, unilateral invasive breast carcinoma between 48 and 79 years with a life expectancy of 10+ years within 365 days of surgery	2437	5.0	Control	Dietary Intervention

Nielsen 2006	Women who underwent total mastectomy and partial axillary dissection under the age of 70 who had high risk of recurrence including one of: tumor >5cm, positive lymph nodes, invasion of skin or pectoral fascia. Women underwent systemic treatment (CMF if premenopausal and tamoxifen if postmenopausal)	3083	18.0	No radiation	Radiation
Fisher 1996	Women with primary operable breast cancer, lymph node negative, estrogen receptor positive, age less than 70 who completed 5 years of adjuvant tamoxifen and who remained disease free.	2818	10.4	Tamoxifen x 5 years followed by placebo	Tamoxifen x 5 years followed by tamoxifen x 5 years
Galimberti 2013	Patients with invasive breast cancer up to 5cm and one more micrometastatic foci (<2mm) in the sentinel nodes, of any age.	931	5.0	ALN dissection	No ALN dissection
Hackshaw 2011	Women with early breast cancer (T1-3, N0/N1, and M0) confined to one breast who were taking tamoxifen for 2 years with no recurrence	3448	10.1	Tamoxifen x 2 years	Tamoxifen x 5 years
Ingle 2006	Postmenopausal women with node negative, tumor > 2cm of any age or age 65+ node-positive and T1 with estrogen receptor positivity	514	11.4	Tamoxifen x 5 years	Tamoxifen + Fluoxoy
Ingle 2008	Postmenopausal	5170	5.3	Placebo x 5 years	Letrozole x 5 years

	women with breast cancer that was ER and/or PR positive, with or without lymph node involvement, who received 5 years of adjuvant tamoxifen on MA-17 study.				
Jakesz 2002	Premenopausal women with resected stage I or II unilateral breast carcinoma with clear margins and level I and II axillary dissection, ER and/or PR+	1034	5.0	Endocrine (tamoxifen x 5 years plus goserelin x 3 years)	Chemo (CMF x 6 cycles)
Jakesz 2007	Postmenopausal women with surgical treatment for ER and/or PR positive primary unilateral stage I or II breast cancer +/- lymph node involvement who completed the ABCSG Trial (5 years of adjuvant tamoxifen) and remained disease free	852	5.2	No additional treatment	Anastrozole x 3 additional years
Kunkler 2013	Patients 65 years or older who underwent breast conserving therapy with T1-2 (up to 3cm), N0, M0, hormone receptor positive invasive breast cancer, with clear excision margins with up to one high risk feature (Grade III or LVI)	1326	5.0	Radiation	No Radiation
Poggi 2003	Patients with a single unilateral stage I or II invasive carcinoma of the breast	237	18.4	Mastectomy	Breast conserving therapy plus radiation
Rustqvist 2007	Postmenopausal women aged 70 or less with early stage unilateral invasive breast cancer	2738	18.0	No Tamoxifen	Tamoxifen x 2 years

Ryden 1995	Premenopausal patients with stage 2 primary breast cancer	429	5.7	Control	Tamoxifen x 2 years
Tinterri 2013	Postmenopausal women between the age of 55 and 75 with unifocal invasive carcinoma of the breast less than 2.5cm with up to 3 positive lymph nodes	749	9.0	BCT alone	Breast conserving therapy/radiation
Veronesi 2002	Patients with infiltrating breast carcinoma no larger than 2cm	701	20.0	Mastectomy	Breast conserving therapy/radiation
Veronesi 2006	Stage I invasive breast cancer or DCIS (which accounted for approx. 1% of subjects) who received no adjuvant therapy diagnosed within the last 10 years	1739	14.6	Control	Fenretinide x 5 years

3.2 Critical Appraisal of Studies of Disease Prognosis

An RCT is considered to be of the highest quality of evidence. However, the quality of an RCT can be downgraded if the risk of bias is serious due to compromise in the study's internal validity. The internal validity reflects the degree to which observed findings reflect true effects of the intervention rather than artifact (Campbell, 1996) and is related to the quality of the study's research methodology. Alternatively, the external validity of a study refers to the extent to which a study's results can be generalized to a population of interest. It is important to examine both the internal and external validity of each study incorporated in a meta-analysis in order to interpret whether the results of the meta-analysis are based on high quality

data and therefore reliable and whether they are applicable to the clinical setting of interest.

The Department of Clinical Epidemiology and Biostatistics at McMaster University (Department of Clinical Epidemiology and Biostatistics, MUHSC) has previously proposed guidelines for examining the internal and external validity of studies which are specifically related to prognosis (Table 2).

Table 2 Guide for assessing articles about clinical course & prognosis of disease (*Department of Clinical Epidemiology and Biostatistics at McMaster University*)

Was an inception cohort assembled?
Was the referral pattern described?
Was complete follow-up achieved?
Were objective outcome criteria developed and used?
Was the outcome assessment “blind”?
Was adjustment for extraneous prognostic factors carried out?

3.3 Critical Appraisal of Included Studies

Using the criteria proposed by the Department of Clinical Epidemiology and Biostatistics at McMaster University, each of the studies included in this meta-analysis have been critically appraised for internal and external validity relevant for studying disease prognosis. The results of the critical appraisal are listed in Table 3 and are discussed in more detail below. A study was considered to be of excellent quality if 4 out of 4 criteria were met; good quality if 3 criteria were met; fair quality

if 2 criteria were met; poor quality if 1 or 0 criteria were met. Of note, there a total of 4 criteria were used instead of 6 because blinding and adjustment were excluded due to reasons discussed below.

Table 3: Critical Appraisal of Included Studies

Study	Inception Cohort	Referral Pattern	Follow-up	Objective Outcomes	Blinding	Overall Score
ATAC 2008	+	-	+	+	+	Good
SBCCG 1996	+	+	+	+	-	Excellent
GIVO 1994	+	+	+	+	-	Excellent
Alkner 2009	+	+	-	+	-	Good
Arriagada 1996	+	+	-	+	-	Good
Arriagata 2002	+	+	+	+	-	Excellent
Chlebowski 2006	+	+	+	+	-	Excellent
Nielsen 2006	+	+	+	+	-	Excellent
Fisher 1996	+	+	+	+	+	Excellent
Galimberti 2013	+	-	+	+	-	Good
Hackshaw 2011	+	-	+	+	+	Good
Ingle 2006		-	-		-	Fair

	+			+		
Ingle 2008	+	+	+	+	+	Excellent
Jakesz 2002	+	-	+	+	-	Good
Jakesz 2007	+	+	+	+	-	Excellent
Kunkler 2013	+	-	-	+	-	Fair
Poggi 2003	+	+	+	+	-	Excellent
Rustqvist 2007	+	+	+	+	-	Excellent
Ryden 1995	+	-	-	+	-	Fair
Tinterri 2013	+	-	+	+	-	Good
Veronesi 2002	+	-	+	+	-	Good
Veronesi 2006	-	-	+	+	-	Fair

3.3.1 Inception Cohort

It is important for a study which examines disease prognosis to enroll a clearly defined inception cohort. That is, a group of patients who are identified at an early and uniform point in the course of their disease. A study which does not include an inception cohort may over- or under-report outcomes of interest. The studies included in this meta-analysis should ideally enroll patients at the time they are diagnosed with early stage invasive breast cancer. Studies where patients are

enrolled prior to diagnosis are not useful for answering the question at hand, and studies where patients are enrolled significantly after the breast cancer diagnosis are likely to under-report the incidence of contralateral breast cancer.

With one exception (Veronesi 2006), each study included an inception cohort where subjects were enrolled at the time of diagnosis of invasive breast cancer. In the study which did not exclusively enroll an inception cohort, approximately half of the patients were enrolled as an inception cohort while the remaining half were enrolled up to ten years after their primary diagnosis. Inclusion of the latter half of the subjects may lead to an under-reporting of the true rate of contralateral breast cancer.

3.3.2 Referral Pattern

Information regarding the specific pathway by which subjects are enrolled into a study is helpful for interpreting the results of a study about disease prognosis. The referral pattern may directly affect the types of patients in a study. For example patients enrolled in a large tertiary center with specialized facilities may present with more complicated cases and higher risk disease than patients who are treated in community centers. Although there is no specific type of referral pattern necessary for inclusion in this meta-analysis, it is useful to know the referral pattern of each study so that the results may be interpreted in the context of the patient population.

The referral pattern was explicitly stated for approximately half (12 out of

22) of the included studies. Alternatively, many of the larger multi-center trials stated the number of centers which participated in the study but did not identify each center individually (ATAC 2008; Galimberti 2013; Ingle 2006; Jackesz 2002; Veronesi 2006). For those which did include referral patterns, there was a range of centers which enrolled patients from small community hospitals to large tertiary centers. This could affect the results and result in selection bias.

3.3.3 Follow-up

All members of the inception cohort would ideally be followed up until the completion of the study in order to avoid missing data as a high proportion of participants lost to follow-up may bias study results. There are various reasons for why complete follow-up may not occur, including death, relocation, or refusal to continue the study. Differences in outcomes amongst those lost to follow-up could affect the overall results particularly when there is an imbalance of participants lost between arms of the study. In addition, a large number of patients lost to follow-up may decrease the power in a study. Although there is no universally accepted loss to follow up rate, a rate of 5% or less is usually considered acceptable whereas a rate greater than 20% is considered problematic (Fewtrell, 2008).

An intention to treat (ITT) analysis is one way to minimize bias due to loss to follow-up. In an ITT analysis participants are analyzed in the groups to which they were randomly assigned regardless of adherence or loss to follow-up (Fisher, 1999) because removal of patients who are lost may alter the balance of characteristics

between the two groups (Sibbald, 1998). Removing patients also reduces the sample size which may decrease the power of the analysis (Heritier, 2003).

There was excellent follow-up in a majority (17 out of 22) of the included studies which had less than 10% of patients lost to follow-up (ATAC 2008; SBCCG 1996; GIVO 1994; Arriagata 2002; Chlebowski 2006; Fisher 1996; Galimberti 2013; Hackshaw 2011; Ingle 2008; Jakesz 2007; Poggi 2003; Rustqvist 2007; Tinterri 2013; Veronesi 2002; Veronesi 2006). The same number of studies also utilized an ITT analysis. However, two studies had greater than 20% of patients lost to follow-up (Alkner 2009; Veronesi 2006), and four of the studies did not mention the number of patients lost to follow-up (Arriagata 1996; Ingle 2006; Kunkler 2013; Ryden 1995).

3.3.4 Objective outcomes

It is important for a study which looks at disease prognosis to define outcomes a priori using objective criteria and to state them in an explicit manner. In evaluating the rate of contralateral breast cancer, an inherently objective outcome, this criterion was met with each study included in this meta-analysis. None of the studies, however, specified that the contralateral breast cancer was diagnosed with histological confirmation. Presumably this was not specified because the standard of care is to diagnose a contralateral breast cancer with tissue biopsy. It is likely that all, or a majority of, the studies required tissue confirmation of diagnosis of contralateral breast cancer.

3.3.5 Blinding

Ascertainment bias occurs when knowledge about the participant's intervention affects study outcomes. The bias may occur from the study administrator, participant, or the outcome assessor. Blinding is a method used to minimize ascertainment bias whereby those involved with the study are unaware of the intervention. A double-blind protocol is ideal where both the study participant and the study investigators are unaware of treatment details (Schulz, 1995).

Only four of the studies included in this meta-analysis implemented a blinding protocol. In many studies, blinding would have been very difficult to implement, particularly in 9 studies which compared patients who did or did not receive chemotherapy, radiation, or surgery (Table 1). However, in these studies where the subjects were not blinded, ideally the adjudication committee would be unaware of treatment allocation.

The risk of bias which results from a lack of blinding is greatest when a patient-reported outcome is being assessed as opposed to an objective outcome (Higgins, 2011), such as contralateral breast cancer. When the outcome is highly objective the requirement for blinding is considered to be less critical because measurement bias should not affect the results. It is for this reason that blinding was removed from the critical appraisal criteria of the studies included in this meta-analysis.

3.3.6 Adjustment

It is important for a study which examines prognosis to adjust for confounding factors that may affect the outcome. In this meta-analysis, however, the crude rates of contralateral breast cancer were extracted from the studies and combined rather than adjusted rates. For this reason, this particular criteria does not apply to the studies in this meta-analysis.

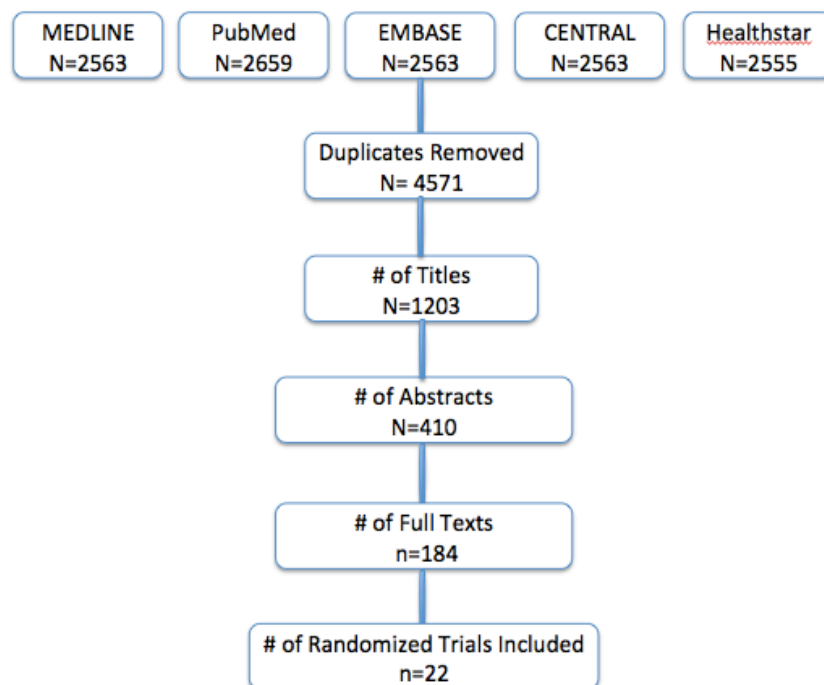
3.4 Summary

In summary, the results of my critical appraisal are that 10 studies were graded as excellent (SBCCG 1996; GIVO 1994; Arriagata 2002; Chlebowski 2006; Nielsen 2006; Fisher 1996; Ingle 2008; Jakesz 2007; Poggi 2003; Rustqvit 2007), 8 as good (ATAC 2008; Alkner 2009; Arraigada 1996; Galimberti 2013; Hackshaw 2011; Jakesz 2002; Tinterri 2013; Veronesi 2002), 4 as fair studies (Ingle 2006; Kunkler 2013; Ryden 1995; Serrazin 1989), and there were no poor studies. Each of the studies will be incorporated into the meta-analysis. A secondary sensitivity analysis will be performed to evaluate the outcome with only studies of excellent and good quality in order to determine whether the fair quality studies biased the results.

Chapter 4: Results

4.1. Search Results

A total of 4571 articles were identified from MEDLINE, PubMed, EMBASE, CENTRAL, and Healthstar after duplicates were removed. Each of these titles were reviewed for potential studies to be included, resulting in 1203 publications. The abstracts of each of these publications were read resulting in 410 potential studies which were considered more extensively with a full text review. There were 184 studies including randomized controlled trials, observational studies, and registries which met the inclusion criteria. Of these, 22 were randomized controlled trials which were then included in this meta-analysis. The initial review was conducted by the primary investigator, PR. The abstracts and full texts were reviewed by PR and SP. The process is illustrated in the following flow diagram:

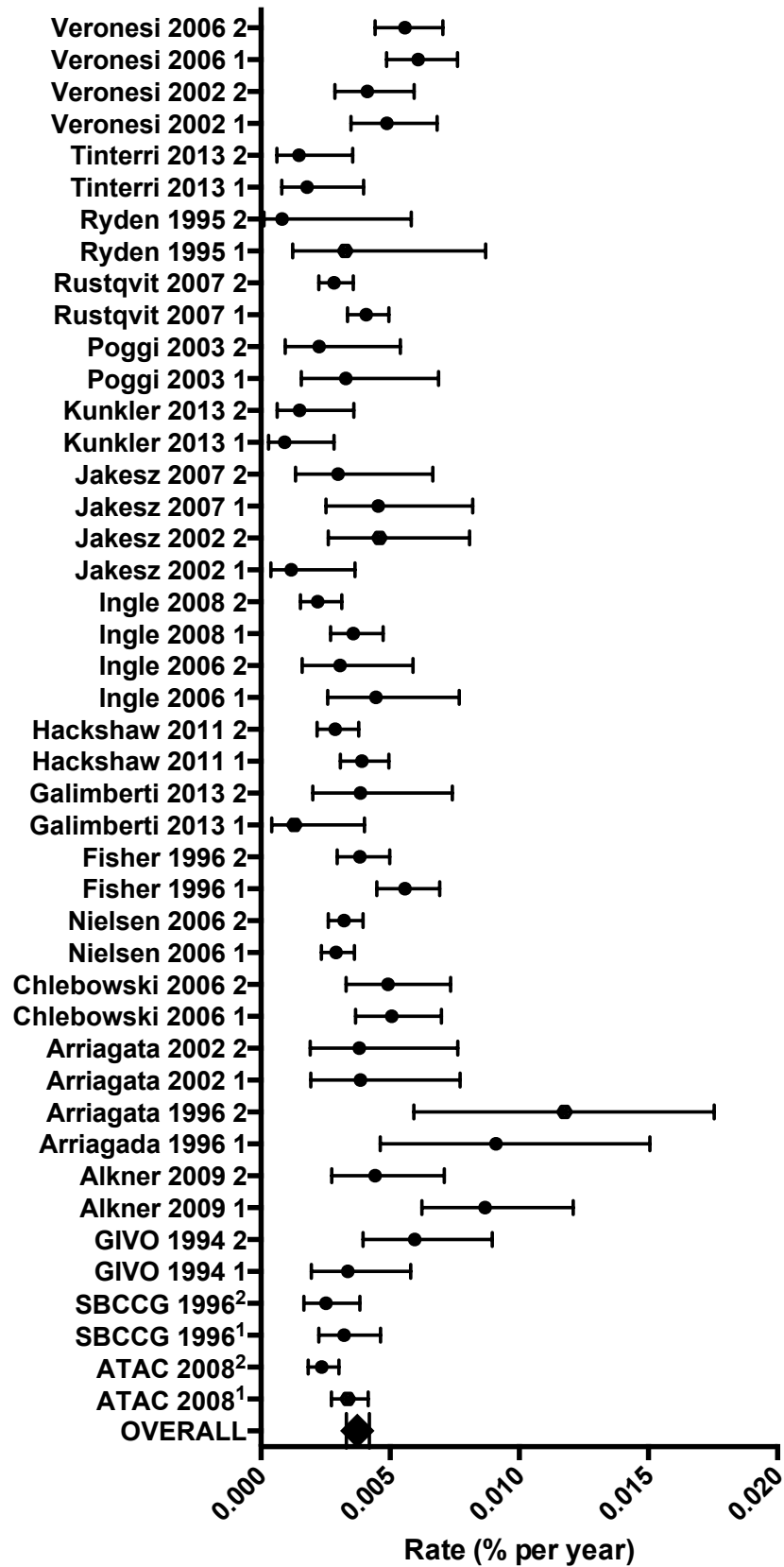


4.2 Assessing for Heterogeneity

4.2.1 The Forest Plot

The following forest plot displays the point estimates of the rate of contralateral breast cancer in 46 study arms included in this meta-analysis. The point estimates appear as point surrounded by error bars which represent the 95% confidence intervals. The x axis displays the rate of contralateral breast cancer per person per year which estimates the annual risk for each patient.

Rates of Contralateral Breast Cancer



A majority of the studies appear to have similar rates of contralateral breast cancer, but two study arms stand out as outliers which have a larger rate than the others. These two arms belong to the same study, Arriagata 1996, Arms 1 and 2. This randomized controlled trial was rated as 'good' according to the critical appraisal conducted in Chapter 4.

In this study, 179 women who presented clinically with a unilateral breast cancer < 20mm in size between the years of 1971 and 1979, were enrolled. The women were randomized to undergo lumpectomy or mastectomy and all women underwent an axillary lymph node dissection. Women with positive lymph nodes (N0, N1a or N1b) underwent a second randomization to receive nodal irradiation versus no further local treatment.

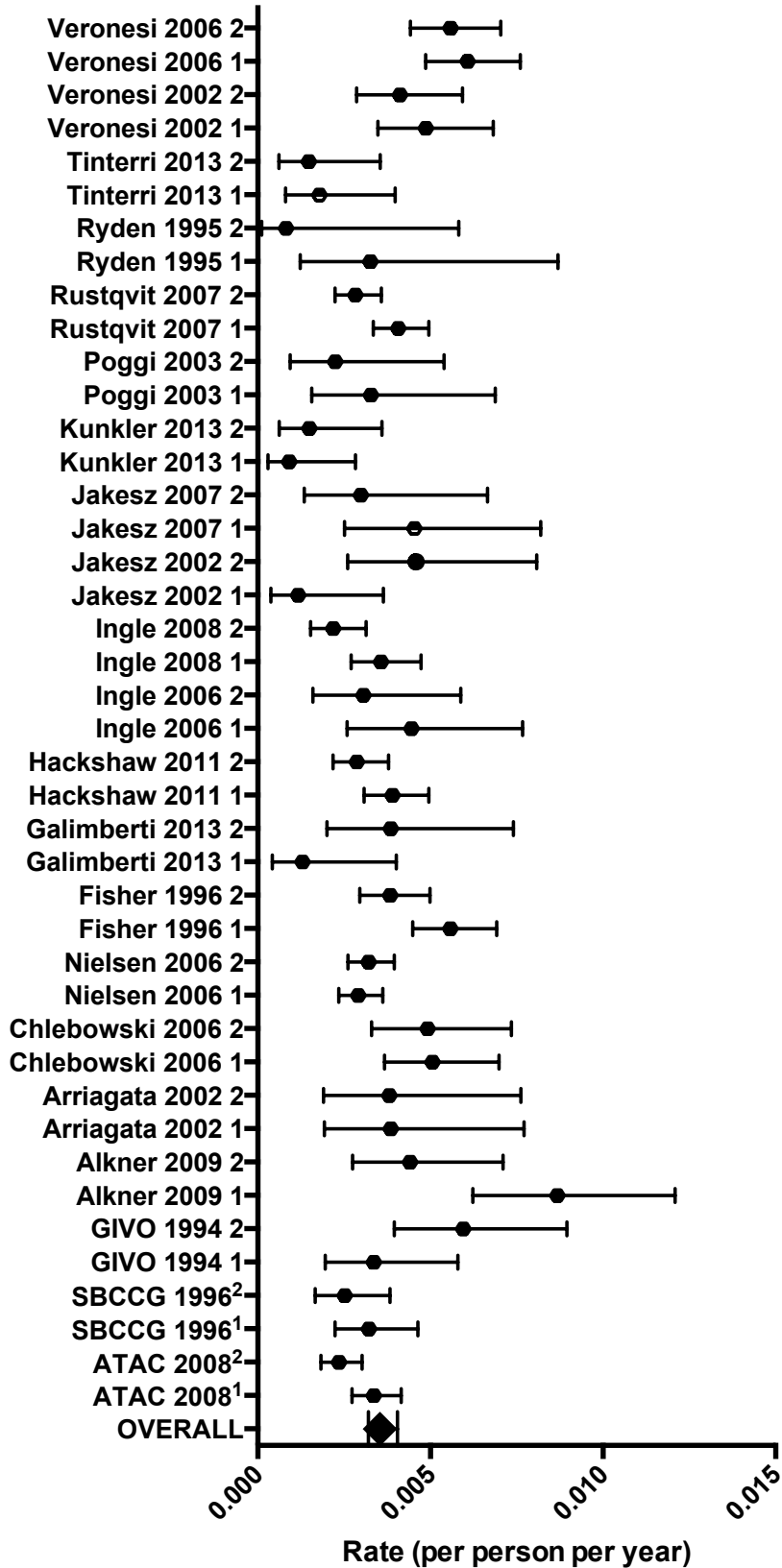
These two study arms are the smallest in the meta-analysis with 88 subjects in the lumpectomy arm and 91 subjects in the mastectomy arm compared to the mean sample size of $n=929$. As a result, the confidence intervals for these arms are very large reflecting a large degree of uncertainty in the effect size.

The enrollment period of this study (1971 to 1979) is the earliest of all studies in the meta-analysis. This may lead to a larger rate of contralateral breast cancer due to suboptimal breast cancer treatment compared to later studies. For example, the lack of adjuvant endocrine therapy in this study likely contributed to an increased rate of contralateral breast cancer. In addition, women who underwent a lumpectomy did not undergo adjuvant radiation unless they had positive lymph

nodes, which would be considered suboptimal by later studies. Of note, this is not unique to this study alone as there are also other studies where the breast cancer treatment would be considered sub-optimal according to the current standard of care. For example, no adjuvant endocrine treatment was offered to patients in Alkner 2009 (Arm 1), Rustqvist 2007 (Arm 1), and Ryden 1995 (Arm 1). Therefore this aspect of the study does not render it to be significantly different from the other studies included in the meta-analysis.

However, based on the small sample size with large confidence intervals, Arriagata 1996 was excluded from the final meta-analysis. The following forest plot displays the final 44 included study arms.

Rates of Contralateral Breast Cancer



Upon visual inspection of the second forest plot, there appears to be greater consistency in rates of contralateral breast cancer compared to the initial forest plot. However, Alkner 2009 Arm 1 has a greater rate compared to the others. This study examined the role of adjuvant tamoxifen in 564 pre-menopausal women with stage II breast cancer who were randomized to 2 years of tamoxifen versus control. The median follow-up was 14 years. In Arm 1, 35 out of 288 women had contralateral breast cancer during the median follow-up of 14 years, compared to 17 out of 275 in the tamoxifen group.

This study was critically appraised to be of good quality. The inception cohort was well defined, as was the referral process, and objective outcomes were applied. However, more than 20% of patients lost to follow-up. The one factor which makes this study different from the others is the patient population, as only premenopausal women were included. It is known that younger women with breast cancer have a more aggressive disease and so it is conceivable that the rate of contralateral breast cancer would be greater in this population particularly without the use of adjuvant endocrine therapy. There may have been patients with BRCA mutations which were yet undetected. This patient population is important to capture and therefore this study has been included in the final meta-analysis.

4.2.2 The Q Test

In this meta-analysis of 44 study arms, the Q test = 174.3 which is greater than the chi-squared reference value of 59.304 for 43 degrees of freedom (MedCalc

[online]]. Please refer to Chapter 2: Methods for background and formulation of the Q statistic. Therefore based on the Q test, the studies are considered to be heterogenous and a random effects statistical model is considered most appropriate for conducting the meta-analysis.

4.2.3 The I² statistic

The I² statistic (described in detail in Chapter 2: Methods) is this analysis = 75.3% which can be interpreted as having considerable heterogeneity. This further supports the findings of the Q test and a random effects model rather than a fixed effects model is the most appropriate to use.

4.3 Results

Using the DerSimonian and Laird method (DerSimonian, 1986) for a random effects model, the rate of contralateral breast cancer from all the studies was calculated in person-year time. The formulation of this method is described in detail in Chapter 2: Method. Excluding Arriagata 1996 as discussed above, there were 42 arms included for the overall analysis:

Study	Group	N	Flup (y)	Events
ATAC 2008	Tamoxifen	3116	8.3	87
ATAC 2008	Anastrozole	3125	8.3	61
SBCCG 1996	Tam 2y	1801	5	29
SBCCG 1996	Tam 5y	1744	5	22
GIVO 1994	Usual f/u	655	5.9	13
GIVO 1994	Surveillance	655	5.9	23
Alkner 2009	No Tam	288	14	35
Alkner 2009	Tam 2y	275	14	17
Arriagata 2002	Tam	415	5	8

Arriagata 2002	Tam+Chemo	420	5	8
Chlebowski 2006	Control	1462	5	37
Chlebowski 2006	Dietary intervention	975	5	24
Nielsen 2006	No Rads	1545	18	81
Nielsen 2006	Rads	1538	18	89
Fisher 1996	Placebo	1414	10.4	82
Fisher 1996	Tamoxifen	1404	10.4	56
Galimberti 2013	ALN dissection	464	5	3
Galimberti 2013	No dissection	467	5	9
Hackshaw 2011	Tam 2y	1724	10.1	68
Hackshaw 2011	Tam 5y	1724	10.1	50
Ingle 2006	Tam 5y	256	11.4	13
Ingle 2006	Txm + Fluoxymesterone	258	11.4	9
Ingle 2008	Placebo	2587	5.3	49
Ingle 2008	Letrozole	2583	5.3	30
Jakesz 2002	Endocrine	511	5	3
Jakesz 2002	Chemo	523	5	12
Jakesz 2007	Nothing	466	5.2	11
Jakesz 2007	Anastrozole	386	5.2	6
Kunkler 2013	Rads	658	5	3
Kunkler 2013	No Rads	668	5	5
Poggi 2003	Mast	116	18.4	7
Poggi 2003	BCT/Rads	121	18.4	5
Rustqvist 2007	No Tam	1364	18	100
Rustqvist 2007	Tam 2y	1374	18	70
Ryden 1995	No Rx	215	5.7	4
Ryden 1995	Nolvadex x 2y	214	5.7	1
Tinterri 2013	BCT alone	373	9	6
Tinterri 2013	BCT+WBI	376	9	5
Veronesi 2002	Mast	349	20	34
Veronesi 2002	BCT/Rads	352	20	29
Veronesi 2006	Control	867	14.6	77
Veronesi 2006	Fenretinide	872	14.6	71

There was a total of 2244 patients included with a mean follow-up of 9.9 years.

There were 1376 events reported. The weighted mean rate of contralateral breast

cancer is 0.360 per 100 person per year with a 95% confidence interval of 0.321 to 0.405 per 100 person per year.

4.3.1 Sensitivity Analysis

This analysis is conducted using only results of studies considered to be of excellent or good quality while fair or poor quality studies were excluded. A detailed critical appraisal with a rating of each study can be found in Chapter 4: Critical Appraisal. A total of 34 arms were included in this analysis:

Study	Group	N	Flup (y)	Events
ATAC 2008	Tamoxifen	3116	8.3	87
ATAC 2008	Anastrozole	3125	8.3	61
SBCCG 1996	Tam 2y	1801	5	29
SBCCG 1996	Tam 5y	1744	5	22
GIVO 1994	Usual f/u	655	5.9	13
GIVO 1994	Surveillance	655	5.9	23
Alkner 2009	No Tam	288	14	35
Alkner 2009	Tam 2y	275	14	17
Arriagata 2002	Tam	415	5	8
Arriagata 2002	Tam+Chemo	420	5	8
Chlebowski 2006	Control	1462	5	37
Chlebowski 2006	Dietary intervention	975	5	24
Nielsen 2006	No Rads	1545	18	81
Nielsen 2006	Rads	1538	18	89
Fisher 1996	Placebo	1414	10.4	82
Fisher 1996	Tamoxifen	1404	10.4	56
Galimberti 2013	ALN dissection	464	5	3
Galimberti 2013	No dissection	467	5	9
Hackshaw 2011	Tam 2y	1724	10.1	68
Hackshaw 2011	Tam 5y	1724	10.1	50
Ingle 2008	Placebo	2587	5.3	49
Ingle 2008	Letrozole	2583	5.3	30
Jakesz 2002	Endocrine	511	5	3
Jakesz 2002	Chemo	523	5	12
Jakesz 2007	Nothing	466	5.2	11

Jakesz 2007	Anastrozole	386	5.2	6
Poggi 2003	Mast	116	18.4	7
Poggi 2003	BCT/Rads	121	18.4	5
Rustqvit 2007	No Tam	1364	18	100
Rustqvit 2007	Tam 2y	1374	18	70
Tinterri 2013	BCT alone	373	9	6
Tinterri 2013	BCT+WBI	376	9	5
Veronesi 2002	Mast	349	20	34
Veronesi 2002	BCT/Rads	352	20	29

The rate of contralateral breast cancer from all good or excellent quality studies is 0.359 per 100 person per year with a 95% confidence interval of 0.319 to 0.403 per 100 person per year. This value is similar to the rate calculated when using all studies, suggesting that inclusion of the studies deemed to be of fair or poor quality did not bias the overall results.

4.4 Subgroup Analysis

Subgroup analyses are done to make comparisons between subgroups of participants. In a meta-analysis subgroup analyses are often done for subsets of studies as opposed to individual participants (Higgins, 2011). There are multiple reasons for why subgroup analyses are done including: a means of investigating heterogeneous results; to answer specific questions about specific patient subgroups or types of interventions or types of studies.

Findings from subgroup analyses must be interpreted with caution as they may not represent a true effect. The following guideline has been proposed to help

evaluate whether an apparent subgroup effect is real or a false positive or false negative result (Higgins, 2011):

Guidelines for Deciding Whether Apparent Differences in Subgroup Response are Real
• Did the hypothesis precede rather than follow the analysis?
• Was the subgroup difference one of a small number of hypothesized effects tested?
• Is the subgroup difference suggested by comparisons within rather than between studies?
• Is the magnitude of the subgroup difference large?
• Is the subgroup difference consistent across studies?
• Was the subgroup difference statistically significant?
• Does external evidence support the hypothesized subgroup difference?

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In this meta-analysis, two subgroup analyses are done as a means of comparing outcomes in particular patient populations: 1) subjects who were not treated with any adjuvant treatment versus those who were treated with systemic adjuvant treatment; 2) subjects who receive post-operative radiation versus those who do not. In addition, a third subgroup analyses examines specifically studies with a minimum 10 years of median follow-up. Each of these subgroup analysis were decided upon a priori and there were no additional subgroup analyses performed. An explanation for why each subgroup was chosen is provided below.

4.4.1 Subgroup Analysis: No Adjuvant Treatment

A subgroup analysis was conducted with study arms in which breast cancer patients did not receive any adjuvant treatment including endocrine, chemotherapy,

or radiation therapy. It was hypothesized that the rate of contralateral breast cancer would be higher in arms with no adjuvant treatment as studies which report outcomes on adjuvant breast cancer treatment have consistently reported lower rates of contralateral breast cancer compared to patients with no additional adjuvant treatment (Fisher, 1989; Early Breast Cancer Trialists' Collaborative Group, 1992).

Five of the arms included in this meta-analysis did not have any adjuvant treatment after being diagnosed with breast cancer.

Study	Group	N	Flup (y)	Events
Alkner	No Tam	288	14	35
Fisher	Placebo	1414	10.4	82
Rustqvit	No Tam	1364	18	100
Ryden	No Rx	215	5.7	4
Veronesi	Control	867	14.6	77

The rate of contralateral breast cancer in arms of studies where no adjuvant treatment was administered is 0.555 per 100 person per year with a 95% confidence interval of 0.400 to 0.769. This is higher than the rate in the 39 remaining study arms where the rate of contralateral breast cancer is 0.349 per 100 person per year with a 95% confidence interval of 0.307 to 0.397. The confidence intervals do not overlap suggesting that the rate of contralateral breast cancer is statistically significantly higher in women with breast cancer who do not receive any adjuvant treatment compared to those who do. This is consistent with our understanding of the risk of contralateral breast cancer from previous studies.

4.4.2 Subgroup Analysis: Adjuvant Radiation

It has been hypothesized that women who undergo radiation may be at a higher risk of contralateral breast cancer due to scattering of radiation onto the contralateral breast (Harvey, 1985). However, previous studies have been inconsistent in their results of this finding (Storm, 1992). I therefore undertook an analysis which includes 5 study arms where patients were administered adjuvant radiation and compared it to studies with no adjuvant radiation.

Study	Group	N	Flup (y)	Events
Nielsen 2006	Rads	1538	18	89
Kunkler 2013	Rads	658	5	3
Poggi 2003	BCT/Rads	121	18.4	5
Tinterri 2013	BCT+WBI	376	9	5
Veronesi 2002	BCT/Rads	352	20	29

The rate of contralateral breast cancer in arms of studies where adjuvant radiation treatment was administered is 0.264 per person per year with a 95% confidence interval of 0.178 to 0.392. This rate is similar to the rate in study arms where patients did not receive radiation (0.296 per 100 person year, 95% CI, 0.204-0.429). Therefore, there is no evidence based on this meta-analysis that adjuvant radiation is associated with an increased rate of contralateral breast cancer.

4.4.3 Subgroup Analysis: Studies with 10+-year Follow-Up

Whether the rate of contralateral breast cancer remains constant over time is unclear. The ideal approach to establish this from a meta-analysis is to combine the

cumulative incidence rates of contralateral breast cancer at certain time-points, e.g. the 5-, 10-, and 20-year marks. The studies included in this meta-analysis, however, do not report cumulative incidence rates, thereby excluding the possibility of such analyses. As an alternative, albeit less than ideal, approach to answering this question, I have undertaken an analysis using only studies with a minimum of 10-year median follow-up (ranging from 10.0 to 20.0 years). If the overall rate of contralateral breast cancer is the same in these studies compared to all studies combined, then this is an indirect method of determining that the rate remains constant even beyond 10 years of follow-up. Alternatively, if the rate of contralateral breast cancer is lower in these studies, this would indirectly suggest that the rate plateaus or declines after at the 10-year point. A total of 22 arms were included in this analysis:

Study	Group	N	Flup (y)	Events
Alkner 2009	No Tam	288	14	35
Alkner 2009	Tam 2y	275	14	17
Nielsen 2006	No Rads	1545	18	81
Nielsen 2006	Rads	1538	18	89
Fisher 1996	Placebo	1414	10.4	82
Fisher 1996	Tamoxifen	1404	10.4	56
Hackshaw 2011	Tam 2y	1724	10.1	68
Hackshaw 2011	Tam 5y	1724	10.1	50
Ingle 2006	Tam 5y	256	11.4	13
Ingle 2006	Txm + Fluoxymesterone	258	11.4	9
Poggi 2003	Mast	116	18.4	7
Poggi 2003	BCT/Rads	121	18.4	5
Rustqvit 2007	No Tam	1364	18	100
Rustqvit 2007	Tam 2y	1374	18	70
Serrazin1989	Mast	91	10	6
Serrazin1989	Lump/Rads	88	10	5

Veronesi 2002	Mast	349	20	34
Veronesi 2002	BCT/Rads	352	20	29
Veronesi 2006	Control	867	14.6	77
Veronesi 2006	Fenretinide	872	14.6	71

The rate of contralateral breast cancer in arms of studies with 10 years of follow-up was 0.412 per 100 person per year with a 95% confidence interval of 0.354 to 0.479. This rate is slightly higher than the overall rate observed in all studies combined, but the confidence intervals overlap suggesting a non-significant difference. This is therefore an indirect method of supporting the concept that the rate of contralateral breast cancer remains stable beyond 10 years of follow-up or perhaps may even increase over time.

4.5 Assessing for Bias in a Meta-analysis

4.5.1. Reporting Bias

Publication bias and selective outcome reporting are two forms of reporting bias. One of the greatest potentials for bias in a meta-analysis is publication bias (Egger, 1998) which occurs when studies with positive results are more likely to be published, are published earlier, and are published in journals with higher impact factors. The odds of publication are reportedly three times greater if the results are positive, which can cause a meta-analysis to overestimate the effect (Easterbrook, 1991).

Selective outcome reporting occurs when studies are excluded from the meta-analysis because the authors did not report the outcome of interest. Selective

outcome reporting can occur if the outcome of interest is considered to be too infrequent to be of significance. Alternatively, the outcome may be large and authors may not wish to disclose it as a secondary outcome.

4.5.2 Heterogeneity

Heterogeneity refers to differences between study results which are beyond those attributable to chance. It occurs because of differences between the studies, including differences in clinical setting or methodology. In this meta-analysis, the Q test and I^2 statistic confirmed the presence of significant heterogeneity and therefore the random effects model was implemented in order to account for some of the heterogeneity.

4.5.3 The Funnel Plot

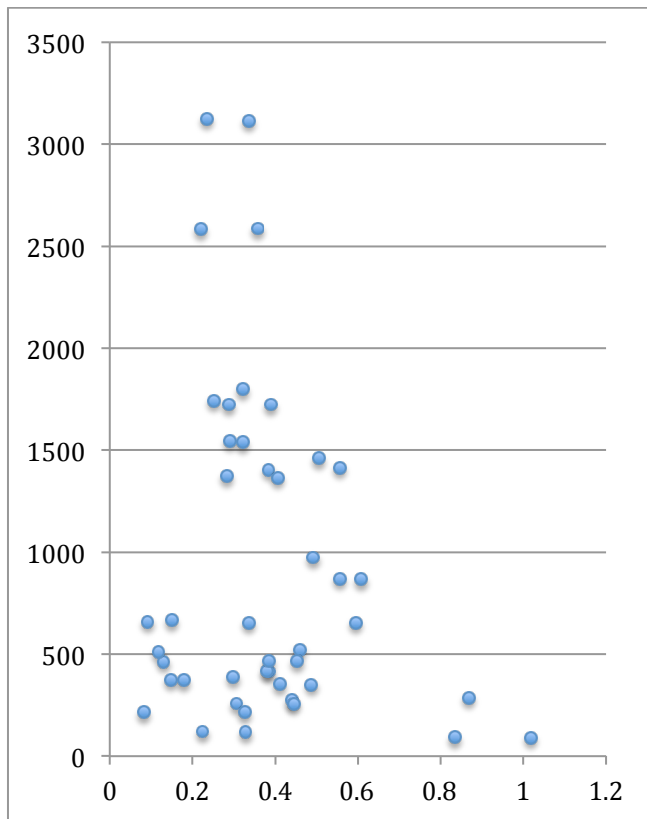
A funnel plot is a simple scatter plot of the rates of contralateral breast cancer from individual studies plotted on the horizontal axis against each study's size on the vertical axis. Effect sizes from small studies scatter more widely at the bottom of the graph, with the spread narrowing among larger studies on top. In the absence of a large amount of bias, the plot should resemble a symmetrical inverted funnel.

Funnel plot asymmetry may occur due to reporting bias or heterogeneity. If smaller studies without statistically significant effects remain unpublished, the funnel plot appears asymmetrical with a gap in a bottom corner of the graph, and this will often be associated with an overestimation of the effect (Egger, 1997). The more pronounced the asymmetry, the larger the amount of bias. However,

publication bias and selective outcome reporting do not necessarily lead to asymmetry in funnel plots. Selective publication and reporting based on the P value may lead to a symmetrical plot in which studies on the extreme right and extreme left are more likely to be published compared to studies in the middle (Higgins, 2011).

In a meta-analysis with heterogeneity where a random effects model is applied, a funnel plot can be expected to be symmetrical but have increased horizontal scatter resulting from the heterogeneity between studies (Sterne, 2011). A large amount of heterogeneity will lead to funnel plot asymmetry if there is a correlation between study size and effect size. For example, smaller studies may include more high-risk populations which may have a greater effect size.

The following funnel plot displays the rates of contralateral breast cancer in each study against the study size:



There is an overall inverse funnel shape with gross symmetry but there is additional horizontal scatter to the bottom right. The studies on the bottom right are those which have a large effect size, or high rate of contralateral breast cancer, and which all appear to have a small sample size. The smaller studies may overestimate the effect and therefore be more likely to be published reflecting a potential publication bias.

Chapter 5: Discussion and Conclusion

The primary question addressed in this meta-analysis, “*what is the rate of contralateral breast cancer in women with early stage breast cancer?*” was answered by combining the results of 22 randomized controlled trials with 40,700 patients using a random effects model. The rate of contralateral breast cancer was found to be 0.36% per year (95% confidence interval, 0.33% to 0.42%). The result was similar when a sensitivity analysis was conducted which examined only excellent and good quality studies suggesting that the inclusion of the 5 studies which were appraised to be fair or poor quality only did not bias the results.

This result is potentially important for both women with early stage breast cancer and their healthcare providers in making an informed decision about the management of the contralateral breast. I embarked upon this project because I observed that a wide range of rates of contralateral breast cancer were being quoted by surgeons and oncologists in discussions with breast cancer patients. Furthermore I had concern that this could be in part influencing the increasing rate of contralateral prophylactic mastectomy. The results of this meta-analysis can be used to help patient and their healthcare team discuss whether the risk of contralateral breast cancer is high enough to warrant a contralateral prophylactic mastectomy. As part of this discussion, it is important for the patient and physician to discuss the risk of contralateral breast cancer in the context of the risk of recurrence from the primary (ipsilateral) breast cancer. For example, in women with axillary node positive breast cancer, the risk of recurrence is at least 50% and for women with

locally advanced stage breast cancer, the risk of recurrence from the primary cancer can be up to 70% which is significantly greater than any the risk of a contralateral breast cancer. It is important for these women to understand that the greatest risk for them is the primary cancer and not the contralateral breast cancer.

A number of secondary a priori questions were also addressed in this meta analysis. The rate of contralateral breast cancer in study arms where no adjuvant treatment was administered was 0.56% per year, significantly higher than the 0.35% per year rate of contralateral breast cancer in study arms where adjuvant systemic treatment was administered. The results of this subgroup analysis are plausible and make biological sense. They are consistent with the results of adjuvant trials that showed that endocrine therapy reduces the risk of both ipsilateral and contralateral breast cancer. The Early Breast Cancer Trialists' Collaborative Group analysis found a decrease of about a third in the incidence of contralateral breast cancer (4.0 versus 6.0 per 1000 per year) (EBCTCG, 2005). Adjuvant chemotherapy was also found to decrease the rate of contralateral breast cancer with a logrank of -23.5 (EBCTCG, 1990).

The rate of contralateral breast cancer in arms of studies where adjuvant radiation treatment was administered was 0.26% per year which was similar to the rate in study arms where patients did not receive radiation (0.29% per year) indicating that adjuvant radiation does not increase the risk of contralateral breast cancer. This finding is consistent with the lack of definitive evidence to support the

hypothesis that adjuvant radiation to the ipsilateral breast increases the risk of contralateral breast cancer.

A very important question is whether the incidence of contralateral breast cancer is constant over time. This question has typically been addressed using data from observational studies because they have long follow-up durations but these studies are limited because of inherent biases. We first examined the rate of contralateral breast cancer in studies with 10 years of follow-up. It was 0.41% per year, which can be translated to a 10-year cumulative risk of breast cancer of 4.1%. This rate is similar to the overall rate in the meta-analysis (0.36% per year), suggesting that the rate of contralateral breast cancer remains constant between 5 and 10 years post diagnosis of breast cancer. However, based on this analysis alone, it is difficult to predict the rate of contralateral breast cancer beyond 10 years of follow-up and whether the rate remains constant or plateaus at some time point beyond the 10 years.

In order to further explore the rate of contralateral breast cancer over time, I have examined the rates in the 4 studies with approximately 20 years of follow-up. The studies included: Veronesi 2002 (20.0 years of follow-up); Poggi 2003 (18.4 years of follow-up); Rustqvit 2007 (18.0 years of follow-up); and Nielson 2006 (18.0 years of follow-up). The weighted mean rate of contralateral breast cancer in these studies with longer-term follow-up is 0.35% per year (95% CI, 0.30% - 0.40% per year). This rate is similar to both the 5-year and 10-year rates of contralateral breast

cancer suggesting that the rate of contralateral breast cancer increases at a constant rate for the first 20 years, yielding a cumulative risk at 20 years of 7%.

The results based on long term follow-up are important clinically in helping a woman with early stage breast cancer, her family and physicians, make an informed decision about the management of the contralateral breast. It is not possible, however, to make inferences from these results beyond 20 years after initial breast cancer diagnosis.

There are several potential limitations to this meta-analysis that will be discussed including study quality, bias, lack of individual level data, and limited follow-up period. It is important to note that a meta-analysis of several small studies does not predict the results of a single large study (LeLorier, 1997). The overall strength of a meta-analysis is influenced by the quality and methodology of the individual studies included rather than the quality of the meta-analysis itself as the bias present in individual studies may bias the results of the meta-analysis. The best evidence synthesis approach has been suggested (Slavin, 1995) whereby the individual studies in a meta-analysis are critically appraised and poor quality studies may be excluded from the analysis. In this meta-analysis, a best evidence synthesis approach was taken as a sensitivity analysis was conducted which included only studies of excellent or good quality methodology. The rate of contralateral breast cancer was found to be similar when the highest quality studies were used, suggesting that inclusion of all the studies did not bias the results.

Sources of bias in a meta-analysis which were discussed in Chapter 4.5

include publication bias, selective outcome reporting, and heterogeneity of studies. Other sources of bias which can occur in a meta-analysis include the lag time bias and the language bias. The lag time bias occurs due to the tendency for studies with positive and striking results to be published earlier than those with non-significant findings (Ioannidis, 1998). The language bias occurs when excluding clinical trials reported in languages other than English effect the results of the meta-analysis (Egger, 1997). Authors have been found to be more likely to publish randomized controlled trials in an English-language journal if the results were statistically significant.

In order to address the reporting bias present in this meta-analysis, it would be ideal to contact the authors of large randomized controlled trials to determine whether contralateral breast cancer was studied as an outcome, but not reported. It is also possible that the search terms used to find articles for this meta-analysis may have missed some relevant trials. There may have been differences in definitions of diagnosis in studies which were not captured.

The present meta-analysis is based on aggregate data rather than individual patient data. There are several advantages to meta-analysis based on individual data, which is considered to be of the highest standard of meta-analysis (Lyman, 2005). There are several advantages to conducting an analysis based on individual level data compared to aggregate data. Individual data allow for completing a time-to-event analysis which may give different results compared to estimating person-years (Stewart, 1995) which was done in this meta-analysis. Related to this point is

that individual data allow for calculating the pattern of the rate of events, e.g. constant hazard or some other function.

In this meta-analysis, the performance of subgroup analysis was limited as a result of lack of individual patient data. Ideally, it would be important to examine the risk of contralateral breast cancer based on specific patient or tumor characteristics, including patient age, family history, tumor histology and grade, but this was not possible with aggregate data.

It is interesting however that the majority of cancer related meta-analysis are based on aggregate patient data due to the considerable resources, years of study, and collaboration with the study investigators to obtain patient level data which are required for individual patient data (Lyman, 2005). One exception is the Oxford Overview in breast cancer where information was sought for every woman in each eligible randomized trial regarding allocated treatment, age, menopausal status, lymph node status, and estrogen/progesterone receptor status.

It is unclear from previous literature what the temporal trend for contralateral breast cancer is. In this meta-analysis, an assumption was made that the risk remains constant over time as this is a trend which was been observed in some of the population based studies which examine the rate of contralateral breast cancer in women for up to 20 years of follow-up, showing rates between 12-15%. However, there is a need for more prolonged follow-up, particularly for young women with breast cancer for whom it is important to understand the cumulative lifetime risk of contralateral breast cancer, ie at 30-, 40-, and even 50-years of

follow-up. In this present analysis, the risk of contralateral breast cancer remained constant in studies with 5-, 10-, and 20-year follow up. If this risk continues to remain constant over time, women who are diagnosed in their early 30's would have a 14% risk of contralateral breast cancer by the age of 70 and 18% by the age of 80. Young women may consider this risk to be sufficiently large to warrant a contralateral prophylactic mastectomy. Alternatively, if the risk plateaus at a time point after 20 years, the lifetime risk may remain below 10% and may not be considered sufficiently large for a contralateral prophylactic mastectomy. Therefore understanding the long-term and lifetime risk of contralateral breast cancer is of utmost relevance in making the decision about contralateral prophylactic mastectomy.

As there are currently no randomized controlled trials which examine the risk of contralateral breast cancer with 30- or 40-year follow-up, a meta-analysis of observational studies is an alternative approach to evaluate the temporal trends. Registries and long-term cohort studies may be the best approach possible at this time to estimate a longer-term risk of contralateral breast cancer. My literature search resulted in 133 observational studies which met inclusion criteria and therefore a much larger patient population would be included in such a meta-analysis. Many of the observational studies had longer follow-up time compared to the randomized controlled trials. In the interest of limited time and resources, this analysis was not undertaken, but it would provide a unique look at the temporal trends of contralateral breast cancer over a longer time period. This will be the

subject of further research.

Among breast cancer survivors, developing a new malignancy in the contralateral breast is the most frequent second-cancer event (Curtis, 2006). The rate of contralateral breast cancer for women with early stage breast cancer has previously been studied in individual studies but rates have varied. This meta-analysis combined the data from randomized controlled trials and found that the risk of contralateral breast cancer for women with early stage breast cancer is 0.36% per year and remains constant for the first 10 and 20 years after initial diagnosis. The rate is higher in women who do not receive any adjuvant systemic therapy, but is not higher in women who have adjuvant radiation. These data are particularly applicable to healthcare providers and patients in making decisions about whether or not to opt for a contralateral prophylactic mastectomy.

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