Breast Cancer Survival by Teaching Status of the Initial Treating Hospital

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Abstract

The objective of this study was to compare survival outcomes of women initially treated at teaching hospitals with those initially treated at community hospitals. The study cohort consisted of 938 women with confirmed node-negative breast cancer randomly selected from among those diagnosed in Ontario in 1991. Cox's proportional hazards model was used to control for the effect of patient and tumour characteristics and treatment received.

Crude 5-year survival for women initially treated at teaching and community hospitals was 92.5% and 88.7% respectively (p=0.067). Among women with tumours ≤20mm there was a 53% reduction in relative risk for women initially treated at teaching hospitals as compared to community hospitals, after controlling significant confounders. A significant survival difference was not apparent among women with tumours > 20mm. There are a number of possible explanations for these findings: patient populations may differ with respect to factors not controlled for in the analysis; there may be misclassification of cases with respect to tumour characteristics; or there may be differences in treatments administered.

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List of Abbreviations

BCS	Breast conserving surgery
CCO	Cancer Care Ontario (formerly, the Ontario Cancer Treatment and Research Foundation)
CI	Confidence interval
CT	Chemotherapy
DCIS	Ductal carcinoma in situ
ER	Estrogen receptor
GRLS	Generalized Iterative Record Linkage System
HT	Hormone therapy
ICD-9	International Classification of Diseases, Revision 9
LVN	Lymphatic, vascular or neural
NSABP	National Surgical Adjuvant Breast and Bowel Project
OCR	Ontario Cancer Registry
OR	Odds Ratio
PMH	Princess Margaret Hospital
PR	Progesterone receptor
RT	Radiation therapy
SES	Socioecomonic status
TNM	Tumour size, node, metastasis

Table of Contents

Table of Contents (continued)

List of Tables

List of Tables (continued)

List of Figures

CHAPTER 1: RATIONALE

Breast cancer represents approximately 30% of all incident cancer cases diagnosed among women in Canada. It has been estimated that in 1989 7,600 women in Ontario will be diagnosed with breast cancer and in the same year an estimated 2,000 women will have died from breast cancer (National Cancer Institute of Canada, 1998). While there has been only a slight decrease in mortality rates over the past decade, incidence rates have increased, possibly as a result of increased screening efforts. Since 1985, age-standardized rates of breast cancer incidence in Canada have increased by approximately 2% per year (National Cancer Institute of Canada, 1997). Over half of all newly diagnosed cases of breast cancer will be node-negative (Harris, 1991).

Regional variations in breast cancer treatment and survival have been documented in a number of countries, as have differences in survival by socio-economic status (Farrow *et al.*,1992; Nattinger *et al.*, 1992; Karjaleinen and Pukkala, 1990). These variations in patient outcome may be accounted for by any number of intermediate factors such as differences in stage at diagnosis, referral and treatment patterns, or differences in health status as a result of dietary or environmental factors.

A few studies have explored the possibility that differences in outcome may be due to differences in hospital or physician characteristics (Karjalainen, 1990; Basnett *et al.*, 1992; Bonett *et al.*, 1991; Gillis and Hole, 1996; Sainsbury *et al.*, 1995; Lee-Feldstein *et al.*, 1994). In particular, studies looking at survival in relation to type of treating hospital (Karjalainen, 1990;

Basnett *et al.*, 1992) and treatment by specialist surgeons (Gillis and Hole, 1996; Sainsbury *et al.*, 1995) have found differences in survival. While some of the variation may be explained by differences in patient populations or differences in treatment, there is some variation which remains unexplained. Within Ontario, researchers have found differences in the type of surgery performed by region and by hospital (Iscoe *et al.*, 1994), differences in patterns of radiation therapy use (Whelan *et al.*,1993), as well as differences in opinion as to how breast cancer patients should best be managed (Sawka *et al.*, 1995).

Teaching status of the initial treating hospital may explain some of the variation in survival. The mechanism may stem from different standards for breast cancer treatment or from the multi-disciplinary setting of the teaching hospital. Access to a greater base of expertise, as provided by the multi-disciplinary setting, may make it possible to explore a wider range of treatment options and may facilitate patient management and follow-up. The volume and outcome relationship, which has been documented in a number of treatment areas, could also potentially be a factor. As well, the patient's initial contact with the system could determine future referrals and future patterns of care. Patterns of referral may also differ by patient characteristics, such as socioeconomic status.

Population based strategies for optimizing the use of available resources and improving equity in health care require a better understanding of the extent to which any of these factors are associated with variations in survival. Understanding the sources of variation will help direct efforts in research and policy to areas where they will make the greatest difference.

CHAPTER 2: STUDY OBJECTIVES

The primary objective of this study is to compare survival of women with node-negative breast cancer who received surgery in teaching hospitals with those who underwent surgery in other hospitals after 5-years of follow-up, using a retrospective cohort study design.

Specific objectives include:

1. To characterize node-negative breast cancer cases initially seen at teaching hospitals and at non-teaching hospitals by patient, tumour, and treatment characteristics:

    - patient characteristics - age, median family income, urban/rural residence, and proximity to the nearest radiation therapy facility
    - tumour characteristics - tumour size, grade, hormone receptor status, multifocality, extent of ductal carcinoma in situ, and lymphatic, vascular or neural invasion
    - treatment characteristics - type of surgical procedure, use of radiation therapy, use of chemotherapy, and use of hormone therapy.

2. To determine if survival of patients initially treated in teaching hospitals is significantly different from survival of patients initially treated at non-teaching hospitals, when controlling for the effect of potential confounders.

The null hypothesis is that no significant survival difference exists between patients initially treated at teaching and at non-teaching hospitals.

CHAPTER 3: LITERATURE REVIEW

The following sections provide a summary of factors which may be associated with survival from node-negative breast cancer, specifically: incidence and early detection in relation to patient characteristics, clinical prognostic factors, and treatment options. The later sections will review studies to date which have examined variations in process of care by treatment setting and variation in survival by treatment setting.

3.1 Incidence and Diagnosis of Breast Cancer

Women in North America have an estimated 7-10% probability of developing breast cancer over their lifetime. The risk is greater for women with identified risk factors. Established risk factors include age, family history of breast cancer, age at menarche and menopause, parity, age at first pregnancy, weight, alcohol consumption, radiation exposure, previous benign breast disease, use of hormone replacement therapy, and possibly diet (Carbone *et al.*, 1995; Harris *et al.*, 1993; Casciato and Lowitz, 1988; Jacobsen and Lund, 1990). Breast cancer also appears to be a disease of the affluent, with women in the higher socioeconomic groups, as measured by income, occupation, or level of education, experiencing close to a two-fold increased risk (Van Loon *et al.*, 1995; Farley and Flannery, 1989; Rimpela and Pukkala, 1987).

Screening and Early Detection

The avenues by which breast cancer can be detected include physical examination by a health professional, self detection and help seeking by the individual, and screening via mammography and palpitation. While some studies looking at symptom recognition and help seeking behavior

among women with breast cancer have concluded that younger women and women in lower SES groups experience longer duration of symptoms (Richardson *et al.*, 1992), other studies have found no difference in help seeking behavior by age or between socioeconomic groups once symptoms are evident (Mor *et al.*, 1990; Lauver *et al.*, 1995).

Increased utilization of breast cancer screening, on the other hand, has been consistently related to urban residence and higher SES (Mercer and Goel, 1997; Reeves *et al.* 1995; Roberts *et al.*, 1990; Wilcox and Mosher, 1993). A study looking at screening in Ontario and the U.S. found that in Ontario, women in the higher income groups (>US$45,600) were 1.8 times (95%CI: 1.6-2.2) as likely as women in the lowest income group (<US$15,200) to receive mammography screening (Katz and Hofer, 1994). Women in the higher income groups were also 2.1 times (95%CI: 1.6-2.8) as likely to receive a clinical breast exam. The study also found differences in screening rates between women living in urban versus rural areas. Other factors which have been significantly related to screening attendance are physician recommendation (Ross *et al.*, 1994; Grady *et al.*, 1992) and beliefs about the efficacy of early detection and treatment (Thomas and Fick, 1995; Michielutte and Biesker, 1982).

In line with these findings, a number of studies have shown that women in lower SES groups and women living in rural areas tend to be diagnosed with more advanced breast cancer than their counterparts (Bryant and Mah, 1992; Wells and Horm, 1992; Richardson *et al.*, 1992; Mandelblatt *et al.*, 1991).

Women whose disease is identified via screening appear to experience better survival than those whose cancers are identified after they become symptomatic (Tabar *et al.*, 1989; Shapiro *et al.*, 1985). Reasons for the observed difference may be attributed to: effective intervention at an earlier stage of disease leading to better outcomes; detection of diseases which are relatively benign or which would have had better outcomes irrespective of treatment; selection bias in the population being screened; or an artifact of lead time bias.

3.2 Prognostic Indicators in Breast Cancer

3.2.1 Clinical Prognostic Indicators

A number of factors are known to be related to patient outcomes and a number of others are under investigation. These factors are interrelated but contribute independently to predicting patient outcomes either because they provide a measure of response to therapy or an indication of the aggressiveness of the disease.

Staging systems have developed over time which group cancer patients into prognostically similar groups in order to guide treatment decisions and estimate prognosis. The most commonly used is that developed by the International Union Against Cancer (UICC) and the American Joint Committee on Cancer Staging and End Results Reporting (AJC) which is based on the TNM (tumour size, node, metastasis) system and classifies patients based on clinical presentation, i.e. physical exam and diagnostic tests (see Table 1).

Table 1: Relationship of UICC Staging to Lymph Node Involvement and Tumour Size

UICC Stage (3rd Ed, 1989)	Tumour Size	Nodal Status	Metastases
0	In situ	negative	no
I	≤ 2.0 cm	negative	no
II	2.0 - 5.0 cm	negative	no
	0 -5.0 cm	positive (N1)	no
III	> 5.0 cm	negative	no
	any size	positive (N2)	no
	any size with extension to the chest wall or skin	positive or negative	no
	any size	positive (N3)	no
IV	any size	positive or negative	yes

*N1-N3 indicate different levels of nodal involvement

Pathological staging differs from clinical staging in that it is based on information obtained from surgical resection of the tumour and dissection of axillary lymph nodes, and tumour size is based on the invasive component only. Pathological stage can be simplified into Stage I, no involvement of axillary nodes, or Stage II, which is further subdivided based on the number of involved axillary nodes.

While stage classifications serve to create clinically meaningful groups, comparisons over time or between different settings can be problematic. Where diagnostic techniques differ, over time or between locations, the meaning of a particular stage classification may also differ (Feinstein *et al.*, 1985; Greenberg *et al.*, 1991). Within stage groupings there remains a fair amount of heterogeneity; other tumour characteristics obtained through pathological assessment, such as tumour grade and hormone receptor status, provide additional prognostic information. These factors are discussed below.

Lymph Node Status

Involvement of the axillary lymph nodes is currently considered one of the most important prognostic factors for women with breast cancer and is a factor in determining the appropriate course of treatment. The axillary lymph nodes, which provide drainage for the breast, are a principal route for regional spread of breast cancer. Involved lymph nodes reflect the tumour's potential for metastatic spread, although distant metastases can occur in patients with no involved nodes.

Among women with stage I or II breast cancer, ten-year survival of those with negative nodes has been shown to be considerably better than for those with positive nodes, after controlling for other prognostic factors. The absolute difference in survival is 30-40% at ten years (Rosen *et al.*, 1989). Prognosis is related to whether or not the lymph nodes are involved and the number of nodes affected.

Clinical assessment of nodal status is known to have high false positive and false negative rates. The randomized trials of the NSABP Protocol B-04 found clinical estimation of nodal status to be incorrect in 38% of presumed negative cases and 27% of presumed positive cases (Fisher *et al.*, 1981). Similar findings are reported by Van Lancker *et al.* (1995).

With respect to pathological assessment, there remains some debate as to the appropriate extent of nodal dissection, particularly since complications range from mild long-term discomfort to potentially debilitating lymphedema (Harris *et al.*, 1993). Results of the NSABP B-04 trials

suggest that nodal status can be accurately assessed with dissection of 3 to 5 nodes, while assessing the extent of nodal involvement requires dissection of a minimum of 10 nodes (Fisher *et al.*, 1991). Other studies have suggested that a minimum of 10 nodes must be examined to accurately assess nodal status (Sosa *et al.*, 1998; Axelsson *et al.*, 1992; Raabe *et al.*, 1997).

Tumour Size

Although a strong and significant relationship has been documented between tumour size and invasion of the lymph nodes, tumour size is a prognostic factor independent of lymph node status. The probability of metastatic spread is thought to be log normally related to the size of the tumour (Atkinson *et al.*, 1986; Tubiana and Koscielny, 1991; Sivaramakrishna and Gordon, 1997) and has been estimated to be 24% for tumours 1.0 to 2.5 cm and 45% for tumours 2.5 to 3.5 cm (Koscielny *et al.*, 1984).

Among women with node-negative cancers, rates of survival and relapse are related to tumour size. One of the largest studies looking at the effect of tumour size in node-negative patients estimated 5-year survival rates to be 96.3% for tumours less than 2 cm, 89.4% for tumours 2 to 5 cm, and 82% for tumours larger than 5 cm (Carter *et al.*, 1989).

Histopathology and Tumour Grade

Mammary carcinomas are classified as either carcinoma in situ or invasive lobular or ductal carcinomas. Carcinoma in situ are those which are confined within the terminal ducts or lobules.

Invasive ductal carcinomas can be further classified based on morphology and patterns of growth. These are referred to as tumours of a special type. Invasive ductal carcinomas of a special type tend to be less aggressive than those which are poorly differentiated and some are known to have very good prognosis (mucinous, tubular, and papillary). Those with no specific histologic features, which make up the majority of breast cancers, are designated as not otherwise specified (NOS) or of no special type (NST) and generally have poorer prognosis. The extent of intraductal disease associated with an invasive cancer is also of prognostic significance; those with a more extensive intraductal component have a higher rate of recurrence (Harris *et al.*, 1993).

Invasive tumours of no special type can be further classified into prognostically meaningful groups by nuclear or histologic grade. Nuclear and histologic tumour grades provide a measure of the degree of tumour differentiation, i.e. the degree to which they resemble other breast tissue. Tumours which are poorly differentiated are more aggressive and pose an increased risk of distant metastases. While nuclear and histologic grade have prognostic significance, there is some concern regarding the reliability of tumour grading systems (Gilchrist *et al.*, 1985; Delides *et al.*, 1982).

The randomized clinical trials of the NSABP found a significant difference in disease-free and overall survival between patients with good nuclear grade (80% and 93%) compared to those with poor nuclear grade (64% and 84%) (Fisher *et al.*, 1988). Nuclear grade was more significantly related to survival than histologic grade. Similar results have been reported

elsewhere (Rosen *et al.*, 1989; Wong *et al.*, 1992).

Estrogen and Progesterone Receptor Status

Estrogen (ER) and progesterone (PR) receptor status have both been shown to be related to patient outcome when considered individually. The two are closely related but their relative importance is not clear. Hormone receptor status is of significance in planning appropriate treatment since ER positive and PR positive tumours are more likely to respond to endocrine therapy. More recently, ER status is thought to have prognostic significance independent of treatment administered.

Overall and disease-free survival is better among patients with ER positive tumours as compared to those with ER negative tumours. Similar but less notable differences are also found for patients with PR positive tumours. Results of the NSABP trial found ER status to be a more important prognostic factor than PR status (Fisher *et al.*, 1988). The difference in 5-year survival was 10% ($p<.001$) based on ER status and 8% ($p=.002$) based on PR status. When considered together, PR status made no additional contribution. The study also found that patients with unknown ER or PR status had a prognosis equivalent to or better than those with positive ER or PR tumours.

Other Prognostic Factors

Other factors which may have prognostic significance include lymphatic, vascular, or neural (LVN) invasion, which may be an indicator of more aggressive disease and is tied to increased

risk of local and distant recurrence (Rosen *et al.*, 1989) . As well, multifocal tumours and tumours with an extensive in situ component, i.e. if the tumour contains a large non-invasive component that extends into the surrounding tissue, have an increased risk of local recurrence (Harris *et al.*, 1993).

A number of other factors which may also be of prognostic significance are currently being studied. These include proliferative capacity or DNA activity, as measured by the S-phase fraction or the thymidine-labeling index, and growth factors. Etiological risk factors, such as diet and reproductive history, do not appear to be related to survival.

3.2.2 Socio-economic Status as a Prognostic Indicator

An association between survival of breast cancer patients and their socio-economic status (SES), as measured by average annual income or years of education, has been identified in several studies (Karjalainen *et al.*, 1990; Kogevinas *et al.*, 1991; Tomatis, 1990; Schrijvers *et al.*, 1995; Bassett and Kreiger, 1990; Vagero and Person, 1987) including one conducted in Ontario (Mackillop *et al.*, 1997). These studies have found that women in the lower SES groups experience poorer survival than do women in the higher SES groups but reasons for these differences have not been clearly established. Possible reasons include differences in disease stage at diagnosis, patient characteristics, health care access, or differences in referral or treatment patterns.

A number of studies have questioned whether the difference in survival can be attributed to women in the higher SES groups presenting with earlier breast cancer as compared to women in the lower SES groups. Carnon *et* al. found that differences in prognostic factors, specifically tumour size, nodal status, histological grade and estrogen receptor status, were not sufficient to explain the difference in survival by SES (Carnon *et al.*, 1994). A Dutch study by Schirijvers *et al.* found that the observed differences in survival by SES were substantially reduced when stage at diagnosis was controlled for in the analysis (Schrijvers *et al.*, 1995). The study was based in The Netherlands over a period when treatment guidelines were in place. Keirn *et al.* found that within their study cohort, which consisted of women treated at a single institution, there was no effect of SES on survival upon controlling for disease stage (Keirn *et al.*, 1985).

3.3 Treatment of Node-Negative Breast Cancer

3.3.1 Surgical Options

The primary intervention for early stage breast cancer is surgery. Options for surgical management range from breast conserving surgery (BCS) to mastectomy. BCS typically involves excision of the tumour and a margin of disease-free tissue but maintains the general appearance of the breast. Simple mastectomy involves removal of the entire breast, the skin overlying the tumour. Radical mastectomy also involves removal of the pectoralis major and minor muscles and complete dissection of the axillary lymph nodes (Harris *et al.*, 1993).

Until recently, simple mastectomy was the preferred procedure. However, a number of

randomized trials have clearly demonstrated that women with early stage breast cancer receiving BCS experience survival outcomes equivalent to those undergoing more extensive surgeries (Fisher *et al.*, 1995; Jacobson *et al.*, 1995; Arriagada et al, 1996; van Dongen *et al.*, 1992; Blichert-Toft *et al.*, 1992; Veronesi *et al.*, 1990). With the addition of radiation therapy, the two procedures also have equivalent rates of local recurrence. It has been estimated that 80% of women presenting with breast cancer in Canada are candidates for BCS (The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer, 1998). In light of these results, existing guidelines either recommend BCS followed by radiation therapy as the preferred procedure (British Columbia Cancer Agency, 1998; The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer, 1998; National Institutes of Health Consensus Conference, 1991) or recommend that the decision be made by the patient, who should be informed of the risk and benefits of each procedure (Mirsky *et al.*, 1997).

3.3.2 Radiation Therapy

A number of clinical trials have looked at the benefit of radiation therapy (RT) following surgery (Forrest *et al.*, 1996;Veronesi *et al.*, 1993; Liljegren *et al.*, 1994; Fisher *et al.*, 1995), including one in Ontario which was restricted to women with node-negative breast cancer (Clark *et al.*, 1996). They have found consistently that women receiving radiation therapy after BCS or mastectomy had better outcomes with respect to local recurrence than those not receiving RT after similar surgery. Differences in overall survival, however, were not significant.

To increase the power to detect a survival difference, The Early Breast Cancer Trialists' Collaborative Group conducted a meta-analysis of 36 randomized trials which compared the same surgery with and without RT or more extensive surgeries with less extensive surgery followed by RT (Early Breast Cancer Trialists' Collaborative Group, 1995). Survival at 10 years was not significantly different within surgical subgroups or overall (40.3% mortality with RT vs 41.4% without). Although deaths due to breast cancer were fewer among women receiving RT as compared to their counterparts, deaths due to other causes were greater.

While it seems clear that radiation therapy affords more favorable outcomes, there lies considerable room for variation in terms of its administration, i.e. location (whole vs. partial breast), dose (total Gy), and schedule (number and interval of treatments and timing following surgery). There is currently no consensus as to the optimal mode of administration. Each of the studies considered in the meta-analysis reached a similar conclusion but used different fractionation schedules. A survey of 551 women with node-negative breast cancer treated at Ontario Cancer Centers between 1984 and 1989 identified 48 different schedules with varying doses and number of fractions (Whelan *et al.*, 1993). Similar variation was observed in an American survey (Priestman *et al.*, 1989) which looked at treatment administered to women with node-negative breast cancer.

Existing treatment guidelines generally recommend that patients receive radiation therapy following BCS (Whelan *et al.*, 1997; The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer, 1998; British Columbia Cancer Agency, 1998).

While there does not appear to be evidence to indicate the optimal fractionation schedule, the most common schedules are generally recommended. The role of RT in different subgroups of patients continues to be investigated, as does the optimal sequencing of radiation therapy and chemotherapy.

3.3.3 Systemic Therapy

The majority of node-negative disease can be effectively treated by local therapy, with 20-30% expected to recur in the first 10 years of follow-up (Henderson, 1991). Because systemic therapies, particularly chemotherapy, have associated side effects, women with low risk of recurrence generally will not receive systemic therapy. In the case of patients at high risk of recurrence, systemic therapy has been shown to improve disease-free and overall survival (Carbone *et al.*, 1995; Henderson, 1991; Fisher *et al.*, 1989; Mansour *et al.*, 1989). Specific criteria for identifying high risk node-negative patients, however, have not been clearly established.

The type of systemic treatment administered, chemotherapy or hormone therapy, is dependent on menopausal status and hormone receptor status. Women who are premenopausal and at high risk of recurrence will generally receive chemotherapy. Women who are postmenopausal and at high risk will generally receive chemotherapy if the tumour is ER negative and chemotherapy plus tamoxifen if the tumour is ER positive.

A number of randomized trials have shown improved survival among women with node-negative tumours receiving tamoxifen or chemotherapy as compared to those receiving no systemic therapy. In a meta-analysis of 30,000 women enrolled in 55 clinical trials, The Early Breast Cancer Trialists' Collaborative Group found a significant survival advantage at 5 and 10 years for women with unknown or positive ER status who received tamoxifen as compared to those who did not. This benefit increased with longer duration of treatment and was apparent among women with node-negative and node-positive breast cancer. Among those with node-negative disease, the relative reduction in mortality at 5 years ranged from 13% to 25%, for 1 and 5 years duration of treatment respectively. A survival advantage was not apparent for women with ER-negative tumours (Early Breast Cancer Trialists' Collaborative Group, 1998).

With respect to use of chemotherapy, the same group found a 25% reduction in relative risk of recurrence and a 18% reduction in risk of mortality among women with node-negative breast cancer (Early Breast Cancer Trialists' Collaborative Group, 1992). When stratified by age, the effect of chemotherapy on survival was not apparent among those age 70 years or older. As with radiation therapy, there is variation in terms of the type of chemotherapy regimens and agents administered (Early Breast Cancer Trialists' Collaborative Group, 1992; G.I.V.I.O., 1988) as well as in the duration and dose of hormone therapy regimens (Early Breast Cancer Trialists' Collaborative Group, 1998).

Existing guidelines generally recommend that among women with node-negative breast cancer, those with tumours greater than 10mm in combination with negative estrogen receptors, poor

grade or lymphatic and vascular invasion be considered high risk, as should those with large tumours (>30mm) irrespective of other factors (Provincial Breast Cancer Disease Site Group, 1998; The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer, 1998; British Columbia Cancer Agency, 1998). The role of chemotherapy in women at moderate risk of recurrence continues to be evaluated.

3.4 Variation in Process of Care by Treatment Setting

Table 2 provides a summary of studies which have looked at the relationship between treatments administered to women with breast cancer and provider characteristics, such as hospital teaching status, hospital size, and physician specialization. Greater use of BCS has been fairly consistently related to larger hospitals, surgeons with greater caseload and surgeons with academic affiliations. Of the studies which reported on use of radiation therapy following BCS, one found greater use among women seen at teaching hospitals (Basnett *et al.*, 1992) and another found no difference by hospital teaching status (Hand *et al.*, 1991).

Of those which looked at the relationship of Chemotherapy (CT) use to provider characteristics, Basnett *et al.* found that women seen at teaching hospitals were less likely to receive CT if nodal status was negative but were more likely to receive CT if nodal status was undetermined. Of the other two studies, one found greater use among patients seen by surgeons with greater caseload (Sainsbury *et al.*, 1995) and the other found no difference in use by hospital teaching status (Hand *et al.*, 1991).

Table 2: Summary of Published Studies Looking at Variation in Breast Cancer Treatment by Provider Characteristics

Process	Study	Hospital Type	Finding	Results *
MISSING STAGING DATA	GIVIO 1986	Large hospitals (>500 beds)	- more complete pathology data - more complete staging data	(83% vs 76%; p<0.05) (89% vs 83%; p<0.05)
	GIVIO 1986	Hospitals with oncology dept/ward	- more complete pathology data - more complete staging data	(81% vs 66%; p<0.001) (89% vs 74%; p<0.001)
	Raabe 1997	Cancer centre	- less likely to be missing ER status	(25% vs 58%)
	Hand 1991	Teaching hospitals	- no difference in hormone receptor determination (Stage II- IV)	ns
	Hand 1991	Teaching hospitals	- no difference in likelihood of axillary dissection (Stage I and II)	ns
	Basnett 1992	Teaching hospitals	- less likely to perform axillary surgery	(51% vs 71%; p<0.0001)
	Gillis 1996	Specialist surgeon	- less likely to be missing both tumour size and nodal status	(9% vs 19%)
EXTENT OF NODAL DISSECTION	GIVIO 1986	Hospitals with oncology dept/ward	- no significant difference in mean number of nodes sampled	(13.9 vs 14.1; ns)
	Raabe 1997	Cancer centre	- significant difference in the median number of nodes examined	(14 vs 7; p <0.001)
	Gillis 1996	Specialist surgeon	- more likely to sample 4 or more nodes	(90% vs 62%)
DIAGNOSTICS	Basnett 1992	Teaching hospitals Teaching hospitals Teaching hospitals	- greater use of mammography - greater use of liver scan - greater use of bone scan	(OR: 15.6; 95%CI:7.8-32.0) (OR: 14.9; 95%CI:9.4-24.0) (OR: 5.0 ; 95%CI:3.8 - 6.7)
BCS USE	GIVIO 1986	Hospitals with oncology ward/dept	- greater use of BCS in patients <50 years old	(38% vs 19%; p<0.01)
	Samet JM 1994	Cancer centre	- greater use of BCS for localized cancer	(OR:1.24; 95%CI:1.12-1.37)
	Nattinger 1992	Teaching hospitals	- greater use of BCS	(OR:1.4 ; 95%CI:1.3-1.5)
	Satariano 1992	Larger hospitals	- greater use of BCS+RT	(OR:2.13; 95%CI:1.73-2.62)
	Lee-Feldstein 1994	Teaching hospitals	- greater use of BCS	(60% vs 25%)
	Foster 1995	Teaching hospital	- greater use of BCS	(73% vs 22%; p< 0.0001)
	Iscoe 1994	Teaching hospital	- no significant difference in use of BCS	(57% vs 50%; ns)
	Studnicki 1993	Teaching hospital	- greater use of BCS	(58% vs 17%; p=0.001)
RT USE	Hand 1991	Teaching hospitals	- no difference in use of RT after BCS (Stage I & II)	ns
	Basnett 1992	Teaching hospitals	- greater use of RT following BCS	(82% vs 69%)
	Sainsbury 1995	Greater caseload	- greater use of RT (all stages)	(49% vs 38%)
CT USE	Hand 1991	Teaching hospitals	- no difference in use of adjuvant therapy (Stage II)	ns
	Basnett 1992	Teaching hospitals	- no diff in use of CT in node +ve patients	(11% vs 9%)
	Basnett 1992	Teaching hospitals	- less use of CT in node -ve patients	(0% vs19%)
	Basnett 1992	Teaching hospitals	- greater use of CT in patients with nodal status undetermined	(27% vs 3%)
	Sainsbury 1995	Greater caseload	- greater use of CT	(8% vs 4%)
	Studnicki 1993	Teaching hospital	- greater use of CT following NCI alert	--
HT USE	Basnett 1992	Teaching hospitals	- greater use among those 50 or older	(62% vs 54%)
	Sainsbury 1995	Greater caseload	- greater use of HT (all ages)	(35% vs 31%)

* ns= not significant

Of the studies which looked at extent of nodal dissection, two found a significantly greater number of nodes were examined by specialist surgeons (Gillis and Hole, 1996) and surgeons at cancer centers (Raabe *et al.*, 1997) and one found no difference in extent of nodal dissection by specialization (GIVIO, 1986). Studies which report on whether or not axillary dissection was done present conflicting results.

As well, there is reason to believe that academic and community hospitals may differ with respect to extent of staging procedures. Basnett *et al.* found that patients seen at teaching hospitals were much more likely to have undergone specific diagnostic tests. Patients seen at large hospitals, teaching hospitals, and specialized centres were less likely to have data missing on various tumour characteristics, including stage, tumour size, and hormone receptor status.

3.5 Breast Cancer Survival by Treatment Setting

A number of studies have looked at the relation between patient survival and provider characteristics, such as university affiliation, hospital size, surgeon specialization and surgeon caseload. The different characteristics used reflect the fact that the components of specialization which might contribute to survival differences have not been isolated. Six studies have looked specifically at survival among women with breast cancer (see Table 3) and of these three have looked at hospital teaching status. All found more favorable outcomes among women treated at larger or specialized centres though not all were statistically significant. The six studies were carried out in England, Scotland, Australia, Finland and the United States.

In a study looking at geographic variation in survival, Karjalainen found that women resident in university hospital districts experienced better survival than their counterparts (Karjalainen, 1990). Women resident in districts with radiation therapy facilities, however, did not have a survival advantage as compared to those living in other districts. Cases diagnosed between 1970 and 1981 were identified through the Finnish Cancer Registry. Patients were classified based on place of residence into one of 21 hospital districts, all of which had facilities for cancer surgery and five of which encompassed university affiliated hospitals. Radiation therapy facilities were available at four university hospital districts and four other hospital districts. Observed five-year survival rates ranged from 53% to 67% by hospital district. Women resident in university hospital districts tended to be younger and the proportion of localized cases varied by district. Crude rates were indirectly standardized to adjust for differences in age distribution and relative survival rates were calculated to adjust for other causes of death. Upon stratifying by extent of disease, variation among those with localized disease could be explained by differences in age or attributed to random variation but among those with non-localized disease there was variation beyond that which could be attributed to random variation. The study also looked at survival from prostatic cancer and found that regional differences in survival could be explained by patient and disease characteristics.

In a British study, Basnett *et al.* found that women initially treated at a non-teaching centre experienced poorer survival (RR 1.74, 95%CI:1.34-2.27) as compared to those treated at a teaching centre in the same region after controlling for patient age and stage at diagnosis (Basnett *et al.*, 1992). Median follow-up was less than 5 years. Cases initially treated at one of

Table 3: Results of Published Studies Looking at Breast Cancer Survival by Provider Characteristics

Study (Publication)	Year of Diagnosis or Treatment	Study Population	Sample size	Effect of Specialization on Survival		Significant Predictors of Survival
1. Karjalainen (1990)	1970-81	Finland	16678 TOTAL	relative survival was better for patients living in university hospital districts; no difference was observed for patients living in hosp districts with RT facilities		
2. Basnett et al. (1992)	1982-86	England	999 TOTAL			age
			436 teaching	teaching hosp	1.00	stage
			563 non-teaching	non-teaching hosp	1.74* (1.34-2.27)	hospital district
3. Lee-Feldstein et al. (1994)	1984-90	United States	3746 TOTAL	Among women with *localized disease*:		age
			2273 small hosp	small hosp	1.00	tumour size
			889 large hosp	large hosp	0.74* (0.59-0.94)	nodal involvement
			380 HMO	HMO	1.63* (1.16-2.30)	treatment(surg±RT)
			204 teaching	teaching hosp	0.96 (0.54-1.68)	hospital type
			2146 TOTAL	Among women with *regional disease*:		
			1327 small hosp	small hosp	1.00	
			464 large hosp	large hosp	0.74* (0.60-0.91)	
			200 HMO	HMO	0.94 (0.66-1.34)	
			155 teaching	teaching hosp	0.78 (0.52-1.16)	
4. Bonnet et al. (1991)	1980-86	Australia	1073 TOTAL			age
			327 small hosp	small hosp	1.00	tumour size
			396 large public	large public hosp	0.93 (0.68-1.27)	nodal involvement
			350 large private	large private hosp	1.28 (0.94-1.75)	
5. Gillis & Hole (1996)	1980-88	Scotland	3786 TOTAL			age
			2868 non-specialist	non-specialist surg	1.00	SES
			918 specialist	specialist surgeon	0.83* (0.74-0.92)	tumour size
						nodal involvement
						surgeon category
6. Sainsbury et al. (1995)	1979-88	England	12861 TOTAL			age
			1251 <10 cases	<10 cases	1.00	SES
			5826 10-29 cases	10-29 cases	0.96 (0.88-1.04)	disease extent
			1957 30-49 cases	30-49 cases	0.82* (0.74-0.90)	tumour grade
			3827 >50 cases	>50 cases	0.85* (0.78-0.93)	period of diagnosis
						treatment (surg,RT,CT,HT)
						consultant caseload
7. Grilli et al. (1998)	Meta-analysis of first five studies			As defined within each study:	Pooled OR:	
				not specialized	1.00	
				specialized	0.82* (0.77-0.88)	

* significant at 0.05

the two centres between 1982 and 1986 were identified through several sources: hospital activity data, the Thames Cancer Registry, and hospital pathology and diagnostic registers. The teaching centre was in an urban setting and the non-teaching centre was in a rural setting, radiation therapy and chemotherapy were available at both. Women treated at the teaching

centre were younger, presented with more advanced disease, and were more likely to undergo diagnostic tests. Disease stage was assigned using the TNM system and was based on pre- or post-operative data as available from the patient chart. Information on socio-economic status was not available.

Lee-Feldstein *et al.*, in an American study of non-Hispanic white women, looked at survival at teaching hospitals, HMO's, and large hospitals (daily census ≥200) as compared to small hospitals (daily census <200) within an urban setting (Lee-Feldstein *et al.*, 1994). Among women with localized breast cancer, the study found a non-significant risk ratio of 0.96 (95%CI: 0.54-1.68) for teaching hospitals and a significant risk ratio of 0.74 (95%CI: 0.59-0.94) for other large hospitals as compared to small hospitals. Among women with regional disease, there was a non-significant survival advantage among those treated at teaching hospitals (RR=0.78; 95%CI: 0.52-1.16) and a significant survival advantage among those treated at large hospitals (RR=0.74; 95%CI:0.60-0.91) as compared to small hospitals. Factors controlled for in the multivariate analysis were age, tumour size, number of positive lymph nodes, histology, and local therapy (surgery and radiation). Interactions were tested and found to be not significant. The outcome was deaths due to all causes. Teaching hospitals had the youngest patients and were most likely to have patients treated with BCS plus radiation. Tumor size did not differ significantly by hospital type. Socioeconomic status and health insurance indicators were not available.

In a study of 1073 breast cancer cases for which tumour size and nodal status were available, Bonnet *et al.* found no significant difference in 5-year relative survival among women treated at

large public (83%) or large private (77%) hospitals as compared to small hospitals (81%) (Bonett *et al.*, 1991). Cases were identified through the Cancer Registry and women were classified based on diagnosing hospital. Only deaths due to cancer were considered. Relative survival rates were calculated using age and sex standardized rates in the general population of South Australia. Maximum likelihood ratios were used to compare survival curves and Cox's proportional hazards modelling was used to obtain adjusted risk ratios. After controlling for age, tumor size, and nodal status, hospital category was not significant for large public (RR= 0.93, 95%CI:0.68,1.27) or large private (RR=1.28, 95%CI:0.94,1.75) hospitals as compared to smaller hospitals.

A study conducted in Scotland by Gillis and Hole found differences in five and ten year survival in relation to treatment by specialist versus non-specialist surgeons (Gillis *et al.*, 1996). Incident cases were identified through the Cancer Registry for the period 1980 to 1988. Follow-up was also conducted through the Cancer Registry. Surgeons were classified as specialist or non-specialist based on local perception and specialist surgeons were asked to provide names of their patients. In this way 918 of the 3786 cases were classified as treated by specialist surgeons. Patient and disease characteristics, specifically patient age, SES (derived from small area census statistics), tumour size and nodal status, were controlled for in the analysis. After adjusting for case-mix, there was a 16% risk reduction among those seen by specialist surgeons. Difference in survival was most pronounced among younger women and among women with tumours 20 to 39mm in diameter. Tumour size and/or nodal status were missing for approximately one third of the cases; these cases experienced poorer survival and were more likely to be treated by non-

specialist surgeons.

As well, a study by Sainsbury *et al.*, which looked at the effect of treatment patterns and clinician caseload on patient survival in the UK, found that patients treated by surgeons consulting on fewer than 10 new cases per year experienced poorer survival than those treated by surgeons with higher caseloads (Sainsbury *et al.*, 1995). Incident cases were identified for a single Health Authority in the U.K. for the period 1979 to 1988. Clinician caseload was defined as the median number of patients seen as primary consultations per year, averaged over the number of years contributed to the period under study. The study consisted of 12,861 patients treated by 160 physicians. Potential confounders controlled for in the analysis included patient age, SES, tumour grade, and extent of disease, as defined by lymph node involvement and metastases. SES was assigned using an index of affluence and deprivation (Townsend Index) based on small area statistics but the authors do not report what factors are considered in construction of the index. The largest differences in survival were attributed to case-mix. After case-mix adjustment, there was little difference in survival across SES groups. Patients managed by surgeons with annual caseloads greater than 29 patients per year experienced significantly better survival (RR= 0.85, 95%CI: 0.77-0.93) as compared to those managed by surgeons seeing fewer than 10 cases per year. There was also a difference in survival between those managed by surgeons seeing between 10 and 29 cases per year, but this difference was not significant (RR= 0.97, 95%CI: 0.90-1.06). The study also found considerable variation across caseload categories with respect to treatments administered in the nine weeks following diagnosis. Among physicians seeing 10 or more cases per year, proportion of patients receiving

chemotherapy, for example, varied from 0 and 46% and proportion receiving hormone therapy varied from 0% to 86%.

In a review of studies which looked at the effect of specialization on process of care and mortality Grilli *et al.* found that overall, cancer patients cared for in specialized centres had a lower risk of mortality (Grilli *et al.*, 1998). A meta-analysis of five of the six breast cancer studies mentioned above, excluding that by Sainsbury *et al.* (1995), generated a pooled risk ratio of 0.82 (95%CI: 0.77-0.88) for specialized versus not specialized centers, as defined within each study. The study also found that specialized centres were more likely to perform specific diagnostic or staging procedures and were more likely to administer conservative surgical procedures.

3.6 Summary

Studies reporting on the relationship of patient and disease characteristics to specialized versus not specialized centres are few. Of the studies which have looked at similarities and differences between centers, most found that women treated at specialized centers were younger but report no difference in terms of distribution by SES. In terms of tumour characteristics, differences have been noted with respect to extent of missing clinical information but little difference has been noted when tumour characteristics are reported. So while it may be reasonable to expect that patients treated at specialized centres will have different tumour characteristics, this relationship has not been documented with respect to breast cancer.

More attention has been paid to issues of process of care. Here studies have found differences between regions, hospitals, and specialized versus not specialized centres. This variation is not entirely surprising given the present uncertainty which surrounds treatment of women with node-negative breast cancer, particularly with respect to use of systemic therapy. As well, diagnostic and staging procedures, which may determine course of treatment, appear to be more extensively done at specialized centres. Studies have also found that teaching hospitals and other specialized centres alter practice patterns more quickly on the basis of new evidence, including treatment guidelines. It is interesting to note that of the studies which considered differences in survival by SES, those which involved a single institution or which were done in the presence of treatment guidelines did not report a difference in survival upon controlling for patient case-mix.

To date there have been six published studies which have looked at survival of women with breast cancer in relation to provider characteristics. The three studies conducted in Britain and one in Finland found significant differences in survival favoring women treated at specialized centres. One study conducted in the U.S. reported a difference in survival by hospital size but not by hospital teaching status and the one study conducted in Australia found no significant difference in survival by hospital size. The cohorts for these studies were constructed over a six to eleven year period prior to 1990. Information on treatment received was available in only three of the six studies.

CHAPTER 4: METHODS

This study used a previously existing cohort of a random sample of women diagnosed with breast cancer in Ontario in 1991. Teaching status of the initial treating hospital was available on this file. As of part of this thesis the cohort was followed up to the end of 1996 through the Ontario Cancer Registry (OCR) to determine vital status, date and underlying cause of death. For those women known to have died in Ontario, a review of death certificates was done to confirm the woman's date of death and to obtain additional information on cause of death. This chapter will provide an overview of the data sources, a description of the study cohort, definitions of measures of exposure and outcome, and an account of the statistical methods used in the analysis.

4.1 The Ontario Cancer Registry

The Ontario Cancer Registry is a population-based disease registry. The OCR is administered by Cancer Care Ontario, formerly the Ontario Cancer Treatment and Research Foundation, which was incorporated in 1943 by the Cancer Act of Ontario and is supported primarily by the Ontario Ministry of Health (Clarke *et al.*, 1987). Although cancer is legally reportable in some provinces, this is not the case in Ontario. As a result the OCR relies on a passive registration process through which data are collected from existing data sources.

4.1.1 Description of the Database

The OCR captures data on newly diagnosed primary cancers, excluding non-melanoma skin cancers. In general, the OCR considers a second cancer site in the same individual to be

metastatic unless it is clearly shown to be otherwise. Because other cancers rarely metastasize to the breast, breast cancer is always assumed to be a primary site.

Since 1977, the Registry has relied on four major data sources: 1) hospital discharge summaries (in-patient only) which mention cancer as one of the 16 discharge diagnoses; 2) pathology reports from hospital and private labs which include any mention of cancer; 3) records of patients referred to any of the nine Regional Cancer Clinics or the Princes Margaret Hospital; and 4) provincial death certificates with cancer indicated as the underlying cause of death.

Data from all sources except pathology reports are coded at the source and received by the OCR in machine-readable format. Pathology reports are received by the Registry in hard copy form and are coded and entered by OCR staff. Because the source files do not contain a common unique identifier, data from all sources are then processed using well established probabilistic record linkage techniques (Felligi and Sunter, 1969; Newcombe, 1988) to identify records belonging to the same individual. The process is automated and was originally developed using the Generalized Iterative Record Linkage System (GRLS) (Howe and Lindsay, 1981) designed at Statistics Canada. Since 1995, AUTOMATCH linkage software, which employs the same linkage methodology, has been used.

In situations where reports of a single case are received from more than one source, a series of standard case resolution rules are applied to reconcile the data, which may be potentially conflicting (Clarke *et al.*, 1987). These rules were developed by OCR staff and employ medical

logic to determine the most accurate disease site, histology, and date of diagnosis from the source records. Decisions as to which data are captured on the case record depend on the consistency and precision of the reported diagnostic data and the validity and reliability of the data source reporting the data. For example, a data source reporting a more specific disease site will be given precedence over one reporting a more general or 'unspecified' site. If two or more 3-digit ICD-9 site codes are indicated, the site from the more reliable source will be selected. The Regional Cancer Centers and the Princess Margaret Hospital are considered the most reliable data sources followed by pathology reports and then hospital discharge records. Death certificates are considered the least reliable source. Cases which cannot be resolved using the set of case resolution rules are reviewed on a case by case basis by OCR staff.

4.1.2 Reliability and Validity of the Data

Given the mechanism by which cancer cases are reported to the OCR, there is potential for both under-reporting and over-reporting. Under-reporting would occur in cases where the patient is not in contact with any of the systems used for registration, e.g. patients diagnosed and treated on an out-patient only basis, or if the condition was inaccurately coded as other than cancer on the source file. These situations are thought to be minimal in the case of breast cancer patients. Of relevance to this study, because the study considers only outcomes following surgical intervention, we would expect that cases of interest will have had specimens sent to a pathology lab and many will have been admitted to hospital and, therefore, will be known to the OCR via the hospital discharge summaries or pathology reports.

Two indicators of data quality have been traditionally used in assessing the quality of cancer registry data: percent of cases registered by death certificate only, and percent of cases which are histologically verified. Over the period 1980 to 1991, 0.8% of breast cancer cases were registered by death certificate only, which is in line with nationally set standards, and 94.4% of breast cancer cases were histologically verified, which is slightly below that known to be attained by other North American Cancer Registries (98%) (Holowaty *et al.*, 1995).

A study conducted by CCO employed a method of capture-recapture to estimate completeness of cancer registration in the province (Robles *et al.*, 1988). A similar method has been used to estimate the number of births and deaths in developing countries and to estimate the prevalence of certain disorders in human populations. The study, conducted for the period 1976 to 1986, estimated breast cancer registrations to be 97.5% complete (Holowaty *et al.*, 1995).

Over-reporting would occur in situations where a single case is reported via more than one source but the records are not recognized as belonging to the same individual. The case would then be captured twice. This is essentially a limitation of the automated record linkage process. Accuracy of the record linkage procedure is dependent on the discriminating power of the identifiers available for linkage as well as on the quality and completeness of the data available for linkage. In other words, quality of the linkage is dependent on the quality of the data sets being linked. The OCR has estimated over-reporting to be 1.2% for the period 1988-1991.

All cancer sites are coded using the International Classification of Diseases Ninth Revision

(ICD-9) (World Health Organization, 1977). A single three digit level code (174) can be used to identify individuals diagnosed with breast cancer. A fourth digit of the code provides a finer description of the anatomic location of the cancer. By virtue of the registration process, a cancer site is mandatory for enrollment into the OCR; however, approximately 3% of registered cases have sites that are ill-defined or of unknown topography (Holowaty *et al*, 1995).

Place of residence is captured using Ontario Ministry of Health codes and postal codes and reflects the patient's usual place of residence at the time of diagnosis. If more than one source provides data on place of residence, data are taken from the source deemed most reliable. Residential data are missing, at the county level, for 1.8% of reported breast cancer cases in the OCR.

Date of diagnosis is captured as the earliest date reported from among all sources and date of birth is captured as reported most consistently or by the most reliable source. Date of diagnosis and date of birth are available for greater than 99.4% of OCR cases. Indicators of the patient's SES, such as occupation, education, or income, are not available through the OCR.

4.2 Vital Statistics Registrations

The Office of the Registrar-General is responsible for maintaining a register of all deaths occurring in the Province of Ontario. Data are collected using two standard forms: a statement of death, which collects demographic information and place and date of death; and a medical certificate, which is completed by the attending physician at time of death and captures information on place and date of death, circumstances and cause of death, as well as any other significant medical conditions (Rosa Ventresca, personal communication, September 1998). These documents are filed with the Office of Registrar-General and a death certificate is issued. The death certificate is required before the body can be disposed of or transported out of province.

The statement of death and medical certificate are filed with the Division Registrars, ie. the municipal divisions, but coding and checks for completeness are performed centrally by the Office of the Registrar-General. Causes of death are coded by trained medical coders, using ICD-9 coding. If any mandatory data are missing or unclear, follow-up is done via correspondence with the attending physician's office. The data are provided to the OCR in computer-readable format on a regular basis (see section 4.5). Data are not captured on the mortality file for Ontario residents who have died out of province.

4.3 Study Cohort

The cohort used for this study consists of 938 randomly selected node-negative breast cancer incident cases diagnosed in Ontario in 1991. The cohort was originally constructed for a study comparing patterns of treatment in Ontario and British Columbia (Goel *et al.*, 1997). This study will subsequently be referred to as 'the original study'. Information relevant to the study at hand is provided below.

Women in the cohort were identified through the OCR. Of approximately 5700 breast cancer cases registered in 1991, 2917 cases were randomly selected from among those eligible for inclusion. Cases eligible for inclusion were those which met the following criteria: patients with invasive breast cancer (ICD-9 site 174) newly diagnosed in 1991; residents of Ontario at the time of diagnosis; females age 20 to 90 inclusive at time of diagnosis; patients with no previous malignant primary and no previous carcinoma in situ of the breast; and patients who had a minimum survival of 30 days following diagnosis. Overall, this represented a 55% sampling rate of those eligible for inclusion.

Following ethics approval, data pertaining to patient, disease, and treatment characteristics were obtained for each patient. Data items not available through the OCR data base were compiled from a number of sources, including pathology reports, hospital medical records, and through correspondence with the most responsible physician. Abstraction of chart data was performed by a group of certified health-records technicians who were centrally trained and provided with a detailed coding manual. The research coordinator conducted checks for quality assurance

including re-audit of a random sample of charts. Any difficulties were reviewed with the study investigators. Table 4 provides a summary of the data items collected for the original study and the source from which they were obtained.

Additional data obtained from hospital charts were used to further assess eligibility and cases were subsequently excluded if they met any of the following criteria:

- the patient had a previous invasive cancer or breast carcinoma in situ,
- the patient had bilateral breast cancer,
- the patient had non-invasive breast neoplasm,
- the patient had clinical stage IIIB (tumour extending to chest wall or skin) or stage IV,
- nodal status was positive or unknown,
- non-epithelial forms of cancer were present, or
- initial treatment was received out of province.

As well, data for one regional cancer centre (272 cases) and one community hospital (3 cases) were excluded as a result of refusal of the institution to participate.

Individual level measures of SES are not available through the OCR and are not routinely captured in patient charts, the two primary sources of data used to compile the original study cohort. As a result, median neighborhood household income is used. These data were obtained by linking the patient's six character residential postal code at diagnosis, to a census enumeration area or census tract via Statistics Canada's Postal Code Conversion File. Median household income of the patient's census tract or enumeration area was then assigned as

determined from the 1991 census (Wilkins, 1993).

Table 4: Summary of Data Items and Data Sources
Used in Construction of the Original Cohort

Data Source	**Data Items**
Ontario Cancer Registry, supplemented by chart review	patient characteristics: • date of diagnosis • date of birth • sex • place of residence • treating hospital
Statistics Canada (1991 census)	• neighborhood median household income (derived from place of residence)
Pathology reports and clinic notes (hospital chart)	tumour characteristics: • tumour size • tumour grade • margins • hormone receptor status • multifocality • lymphatic, vascular, or neural invasion • extent of ductal carcinoma in situ
Surgical notes (hospital chart)	treatment characteristics: • type of surgical procedure
Cancer Clinic notes and Correspondence with Physician	treatment characteristics: • use of radiation therapy • use of chemotherapy • use of tamoxifen
Canadian Hospital Directory	hospital characteristics: • teaching status • number of beds
Canadian Medical Directory	physician's characteristics: • year of graduation from medical school • academic affiliation

Data initially obtained from the Cancer Registry were supplemented by that obtained from chart review. Date of diagnosis used in this study was that obtained from chart review, which was defined as the date of the first microscopic (histologic or cytologic) confirmation.

4.4 Exposure Ascertainment

Exposure is treated as a point in time event, i.e. patients are classified based on the hospital in which they received initial treatment regardless of where they received subsequent treatments over the period under consideration. The hospital in which the patient underwent most definitive initial surgery was classified into one of two groups according to the 1991 Canadian Hospital Directory (Canadian Hospital Directory 1991-1992, 1991):

1. teaching hospital, or
2. non-teaching (community) hospital.

The Canadian Hospital Directory defines teaching hospitals as those with membership in the Association of Canadian Teaching Hospitals. Criteria for membership, as they were in 1991, are provided in Appendix B. Most definitive surgery is defined as the most extensive procedure for initial local management of the breast cancer within 90 days of diagnosis. Approximately 30% of the cases are classified as having received initial treatment in a teaching hospital and the remaining 70% were classified as having received initial treatment in a community hospital.

4.5 Outcome Ascertainment

Outcomes were ascertained through the OCR, which regularly conducts an automated probabilistic record linkage of cancer incidence records to Ontario mortality records which are provided by the Registrar-General's office. Out of province deaths are not registered by the Registrar-General's office but may become known to the OCR via other sources. Follow-up

was done to the end of 1997, the last complete year for which vital status was available from the Ontario Cancer Registry.

A number of studies have evaluated the sensitivity and specificity associated with using probabilistic linkage to death registrations as a method of outcome ascertainment (Newcombe *et al.*, 1983; Smith *et al.*, 1982). A study comparing individual follow-up to computerized record linkage found computerized record linkage to be a more efficient and more accurate method of ascertaining mortality, even in the presence of inaccurate or incomplete personal identifying data (Shannon *et al.*, 1989). A study by Schnatter *et al.* assessed the validity of death ascertainment for a cohort of Canadian refinery and petrochemical workers via computerized record linkage (using GRLS software) to death registrations. The study estimated the case ascertainment rate for deaths occurring in Ontario to be close to 98% (90%CI:95-99%) . The study found a very low false positive rate and estimated the overall specificity to be 99.8% (Schnatter *et al.*,1990).

Follow-up data obtained from OCR include date of death, single (underlying) cause of death, and death certificate number. Death certificate number was used to retrieve the original death certificate for reasons detailed in the following section.

4.6 Review of Death Certificates

Follow-up via the OCR provided only a single (underlying) cause of death and this was missing for 19 cases. Upon approval from the Office of the Registrar-General, death certificates were reviewed in order to obtain additional causes of death and to assess whether the death was due to cancer or to other causes. Dates of death were also verified. The following process was used in reviewing death certificates.

1. The death certificate was located using year of death and death certificate number, both obtained from the OCR.
2. Birth date was used to verify that the correct death certificate was located. This was the only common personal identifier available.
3. Date of death provided by the OCR was compared to that on the death certificate and any discrepancies noted.
4. Underlying and all secondary causes of death were recorded along with any pre-existing conditions, without reference to cause of death provided by the OCR.
5. If breast cancer was not listed among the causes of death, a note was made of whether or not breast cancer was listed anywhere on the death certificate, as well a note was made of who completed the death certificate (i.e. attending physician, coroner, or other).

Following review of death certificates, an assessment was made of whether or not the death could be attributed to breast cancer. Cases were independently assessed by two reviewers, who subsequently met to resolve any discrepancies. As well, a comparison was made of the two data sources using Cohen's Kappa.

4.7 Analysis

4.7.1 Initial Data Review

Statistical analysis, data manipulation, and graphic presentation were done using SAS statistical software and Microsoft Excel. Summary statistics were generated for all covariates, which are listed and defined in Table 5. Univariate and bivariate statistics were calculated for continuous variables, overall and within exposure groups. Frequency tables and histograms were generated for categorical data, overall and within exposure groups. Coding of variables obtained from the original study are shown in Appendix A.

Table 5: List of Covariates, Definitions, and Number of Missing Values

Covariate	# Missing	Definition
Age	none	Age at diagnosis as calculated from date of birth and date of diagnosis
Median family income	none	Median family income for the neighbourhood (Enumeration Area or Census Tract) in which the patient lived when diagnosed
Urban/Rural residence	none	Patient's residence at time of diagnosis (distinction is based on postal code)
Distance to radiation facility	none	Straight line distance from patient's residence to the closest facility providing radiation therapy
Tumour size	10	Size of the tumour at its largest diameter (in millimeters)
Grade	342	Degree of tumour differentiation
ER Status	160	Estrogen receptor status (positive, negative, missing)
PR Status	161	Progesterone receptor status (positive, negative, missing)
Multifocality	none	Whether the neoplasm had multiple foci (or two or more invasive lesions)
Extent of DCIS	none	Extent of ductal carcinoma in situ with the invasive cancer
LVN invasion	579	Whether or not patient had local invasion of lymphatics, veins or nerves
Type of Hospital	none	Hospital in which patient underwent the most extensive procedure for initial local management of the breast cancer within 90 days of diagnosis
Surgery type	none	Most definitive surgery received within 90 days of diagnosis
Radiation therapy	5	Whether radiation therapy was provided as part of the primary treatment
Chemotherapy	1	Whether chemotherapy was provided as part of the primary treatment
Hormone therapy	22	Whether hormone therapy (tamoxifen, endocrine, or other) was provided as part of the primary treatment
Nodes examined	24	Number of regional nodes examined

Categorizing Continuous Variables

The following continuous variables were categorized based on *a priori* knowledge and, in the case of median income, on frequency distributions: age, tumour size, median income, and number of nodes dissected. Age at diagnosis was categorized as <50, 50-65, or 65-90. Tumour size was categorized as ≤20mm or >20mm, as is used in the TNM classification system to obtain prognostically similar groups (Harris, 1991). Number of nodes examined was classified as <10 nodes or ≥10 nodes, based on recommendations of a number of studies looking at the relationship between number of nodes examined and assessment of nodal status (Sosa *et al.*, 1998; Raabe *et al.*, 1997; Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer, 1998).

Handling Missing Values

The number of missing values for each covariate are also shown in Table 5. Data on patient characteristics, diagnosis date, and initial treating hospital were complete for all records. Missing values were treated one of three ways:

- where only a few values were missing for a particular data item, as was the case for tumour size (n=10), radiation therapy (n=5), chemotherapy (n=1) and hormone therapy (n=22), these were coded as missing, meaning that the records would be excluded from subsequent analyses which involve that particular variable;
- where a particular data item was missing for a large proportion of records, as was the case for grade (36%) and LVN invasion (63%), missing values were treated as a homogenous group; and

- where appropriate, based on clinical rationale and the relationship to the current exposure and outcome of interest, missing values were collapsed into an existing category. This was the case for ER status (n=160) and PR status (n=161) which were grouped with ER and PR positive tumours. The relationship of women with ER unknown tumours to hospital type and survival outcomes is not significantly different from that of women with ER positive tumours. With respect to treatment, women with undetermined ER status are treated similarly to those with known positive receptors in that they will be considered at low risk if the tumour is small and Tamoxifen has been shown to have a beneficial effect for women with both ER positive and ER untested tumours (Early Breast Cancer Trialists' Collaborative Group, 1998). When ER status and PR status were modelled in three categories (missing, positive, and negative), neither missing ER nor missing PR contributed independently in the presence of other tumour variables.

Relationship Between Covariates

The relationship of covariates to one another was examined using contingency tables and a chi-square test for categorical variables. Among the patient variables, urban/rural residence, median family income, and distance to nearest radiation facility were highly correlated. Among the disease variables, tumour size, tumour grade, ER status and PR status were highly correlated. Extent of DCIS and multifocality were also highly correlated. Among the treatment variables BCS and RT were highly correlated.

4.7.2 Survival Time Calculation

Survival time was calculated as the time difference, in years, between date of diagnosis and date of death or December 31, 1996, for those not known to have died during the follow-up period. Date of diagnosis used to calculate survival time was that obtained from chart review. For the analysis of cancer only deaths, patients dying of causes other than breast cancer were censored on their date of death.

4.7.3 Descriptive Analysis

In order to meet the first study objective, summary statistics were generated to compare the characteristics of women initially treated at each of the two hospital types. The relationship of each covariate to the exposure variable (hospital type) was examined by calculating odds ratios and confidence intervals. Chi-square statistics were calculated to determine whether differences in proportions between the two exposure groups could be attributed to random variation.

The relationship of each covariate to the outcome of interest (survival) was examined by modelling each variable individually using Cox's proportional hazards model. The Wald test statistic was used to test for significance. Five-year survival estimates were obtained using product limit estimates and Kaplan-Meier survival curves plotted. Survival curves were compared using the Log-Rank statistic.

4.7.4 Survival Analysis: All Causes Mortality and Cancer Mortality

Multivariate analysis was performed using Cox's proportional hazards model. Hazard ratios were calculated for women initally treated at teaching hospitals as compared to community hospitals (reference category). The analysis was done for all-cause mortality and for breast cancer specific mortality, in which deaths from other causes were censored at time of death.

The following steps were used in building the model:

1. Patient, disease, and treatment variables were modelled on their own to identify significant explanatory factors within each group of variables. Manual backward stepwise regression was used and variables which were highly correlated were further investigated through subset analyses. Variables significant at α=0.10 were retained.
2. Significant variables from the previous three analyses were then assessed collectively. Manual backward stepwise regression and subset analysis was used, with the final model retaining variables significant at α=0.10.
3. Interactions between hospital type and each of the terms in the model were tested for significance. Disease and treatment variables may be related to process of care or extent of disease and could result in an effect modification. Similarly, patient characteristics may be tied to process of care.
4. The final model, including any significant interaction terms, was rerun using manual backward stepwise regression, and only those variables significant at α=0.05 were retained. The models were compared in terms of changes to the risk estimates and standard errors.

Large changes in the standard errors were used to assess collinearity of terms in any given model. Cox's proportional hazards model is a semi-parametric model so that the shape of the underlying hazard is not specified. It does assume, however, that the hazards are proportional over time. The proportional hazards assumption was assessed graphically and with the introduction of time dependent variables into the model.

4.8 Statistical Power

With the 938 cases which comprise the cohort, of which approximately 30% were initially treated at a teaching hospital, and assuming an average five year survival of 85% (Stage I and II), it would be possible to detect hazard ratios of 2.0, 1.7, and 1.6 with powers of 98%, 86% and 76% respectively. This calculation is based on total survival time contributed to the study.

CHAPTER 5: ETHICAL CONSIDERATIONS

Approval for the original study was obtained from Cancer Care Ontario and Sunnybrook Health Sciences Centre. The approved protocol covered retrieval of all records used in the current study.

The current study uses secondary data sources to obtain required data items. No contact was required with individual patients or their physicians. Outcomes were ascertained through linkage with the OCR using record identifiers which were assigned to each individual in the cohort. The OCR prepared a file with the last known vital status of each subject. This file was merged with the clinical information file (which contains no identifiers) using the record number. Approval for access to the appropriate vital statistics documents was obtained through the relevant government Freedom of Information Office.

In order to maintain confidentiality, the analysis file contains no personal identifying data. All results are presented such that individual hospitals or patients cannot be identified.

CHAPTER 6: RESULTS

Of the 938 women in the cohort, 292 (31%) received initial surgery at teaching hospitals and the remaining 646 (69%) at community hospitals. Overall, survival of the cohort at 5 years was 89.9%. The mean age of the cohort was 59.7 years, with women initially treated at teaching hospitals tending to be younger ($\bar{x}$=58 years) than those seen at community hospitals ($\bar{x}$=60 years). The cohort consisted largely of women resident in urban areas of the province (85%) at the time of diagnosis.

Table 6 shows the number of deaths and censored observations for analysis of all-causes mortality and deaths due to breast cancer. The number of deaths which could be attributed to breast cancer are few (70 in total). Descriptive statistics presented (Sections 6.1-6.3) are based on deaths from all causes. Results of multivariate analysis are presented for deaths from all causes (Section 6.4) and cancer only deaths (Section 6.5).

Table 6: Number of Deaths and Censored Observations by Type of Hospital, Deaths From all Causes and Deaths Due to Breast Cancer

Hospital	Number of Observations	Deaths From All Causes		Deaths Due to Breast Cancer	
		Deaths	Censored	Deaths	Censored
Community	646	85 (13%)	561 (87%)	55 (9%)	591 (91%)
Teaching	292	26 (9%)	266 (91%)	15 (5%)	277 (95%)
Total	938	111 (12%)	827 (88%)	70 (7%)	868 (93%)

6.1 Relationship of Patient and Disease Characteristics to Exposure and Outcome

Crude survival estimates, at 5 years, are shown in Table 7 below. Estimates by hospital type show better survival among women receiving initial treatment at teaching hospitals as compared to community hospitals (p=0.067). This difference was apparent, though not statistically significant, over age and income groups. When stratified by tumour size, women with tumours less than 20mm in diameter experienced significantly better survival at teaching hospitals as compared to community hospitals; there was little difference in survival among those with larger tumours. Kaplan-Meier survival curves for each of the stratification variables (hospitals combined) are provided in Appendix C.

Table 7: Five-Year Survival Estimates by Hospital Type, Age, Median Family Income, Tumour Size and Estrogen Receptor Status

Stratification Variable	Five-Year Survival (Product-Limit Estimates)			Log Rank P-value
	Community	Teaching	Difference	
Hospital Type	88.7%	92.5%	3.8%	0.067
Age at Diagnosis:				
< 50	89.9%	94.1%	4.2%	0.212
50 - 65	92.3%	92.6%	0.3%	0.660
65 - 90	84.2%	89.8%	5.6%	0.208
Median Family Income:				
< 45,000	87.8%	89.9%	2.1%	0.300
>=45,000	89.6%	95.4%	5.8%	0.091
Tumour Size:				
<=20 mm	90.6%	95.7%	5.1%	0.006
> 20 mm	84.3%	83.1%	-1.2%	0.514
Estrogen Receptor Status:				
positive/missing	90.9%	95.1%	4.2%	0.065
negative	80.3%	77.2%	-3.1%	0.904

Table 8 provides a summary of patient and disease characteristics as they relate to patient outcomes. As would be expected, significantly lower unadjusted risk ratios were observed for younger patients (<50 and 50-65), patients with smaller tumours (<20mm), well differentiated tumours, and hormone receptor positive tumours. Women living in neighbourhoods with higher family incomes experienced better survival, which was of borderline significance. Urban residence and close proximity to a facility providing radiation therapy were also related to better outcomes but the differences were not significant.

Women missing information on tumour grade experienced outcomes which fell between those observed for women with moderately and poorly differentiated tumours. Women missing data on LVN invasion experienced outcomes similar to that observed for women with no evidence of LVN invasion. Women with unknown ER and PR status experienced outcomes which were better than that observed for women with reported ER and PR positive tumours, although the difference was not statistically significant.

Table 8: Relationship of Patient and Disease Characteristics to Patient Outcome

Variable	Level	Frequencies n	deaths	Risk Ratio	95% Confidence Interval *	Wald Stat P-value
PATIENT CHARACTERISTICS						
Age at diagnosis	< 50	234	21	**0.493**	**0.300, 0.811**	**0.005**
	50 - 65	358	30	**0.458**	**0.295, 0.709**	**0.001**
	65 - 90	346	60	1.000	—	
Family Income	< 45,000	496	68	1.000	—	
	>=45,000	442	43	0.689	0.470, 1.009	0.056
Distance to nearest radiation facility	< 50	852	102	1.000	—	
	>= 50	86	9	0.871	0.440, 1.721	0.690
Residence	urban	800	93	1.000	—	
	rural	138	18	1.130	0.682, 1.871	0.636
DISEASE CHARACTERISTICS						
Tumor size	<=20 mm	647	57	1.000	—	
	> 20 mm	281	54	**2.331**	**1.607, 3.383**	**0.000**
	missing	10	-	—	—	
Grade	well	102	6	1.000	—	
	moderate	308	32	1.815	0.759, 4.341	0.181
	poor	186	30	**2.835**	**1.180, 6.813**	**0.020**
	unknown	342	43	2.168	0.923, 5.096	0.076
Extent of DCIS	invasive	490	68	1.000	—	
	invasive + DCIS	316	33	0.744	0.491, 1.127	0.163
	extensive DCIS	132	10	0.532	0.274, 1.033	0.062
LVN Invasion	no invasion	232	27	1.000	—	
	LVN invasion	109	19	1.524	0.847, 2.741	0.159
	unknown	597	65	0.927	0.592, 1.453	0.742
ER Status	positive	597	61	1.000	—	
	negative	181	41	**2.411**	**1.623, 3.582**	**0.000**
	missing	160	9	0.548	0.272, 1.104	0.092
PR Status	positive	506	49	1.000	—	
	negative	271	53	**2.154**	**1.461, 3.177**	**0.000**
	missing	161	9	0.576	0.283, 1.172	0.128
Multifocality	unifocal	865	103	1.000	—	
	multifocal	73	8	0.878	0.428, 1.803	0.724

* bolded values are significant at 0.05

The relationship of patient and disease characteristics to initial treating hospital is shown in Table 9. Women younger than age 50 were significantly more likely to be initially treated at teaching hospitals as compared to those 65 or older (OR=1.44; 95%CI:1.01-2.06). Women seen at teaching hospitals were significantly more likely to live in close proximity (<50km) to a facility providing radiation therapy (97% vs. 88%). There was little difference in distribution by median household income, with approximately equal distribution between high and low income groups, or the proportions living in rural areas (12% vs. 16%).

Women living in urban areas were less likely to present with large tumours as compared to those living in rural areas, although the difference was not statistically significant. Women living in urban areas were also more likely to be resident in neighbourhoods with higher family incomes.

Women with multifocal tumours and tumours with an extensive in situ component reported were significantly more likely to have receive initial surgery at a teaching hospital. Forty five percent of women initially treated at community hospitals were missing information on tumour grade as compared to 18% of those initially treated at teaching hospitals (OR=0.27; 95%CI:0.20-0.38). Information on hormone receptor status was more often unknown among women initially treated at teaching hospitals (21% vs 15%) but the difference was not significant.

Table 9: Relationship of Patient and Disease Characteristics to Type of Hospital

Variable	Level	Community		Teaching		Chi-sqr	Odds	95% Confidence
		n	%	n	%	P-value	Ratio	Interval **
PATIENT CHARACTERISTICS								
Age at diagnosis	< 50	149	23%	85	29%	0.117	**1.444**	**1.013, 2.058**
	50 - 65	249	39%	109	37%		1.108	0.801, 1.533
	65 - 90	248	38%	98	34%		1.000	---
Family Income	< 45,000	337	52%	159	54%	0.516	1.000	---
	>=45,000	309	48%	133	46%		0.912	0.691, 1.204
Distance to nearest radiation facility	< 50	568	88%	284	97%	0.001	1.000	---
	>= 50	78	12%	8	3%		**0.205**	**0.098, 0.431**
Residence	urban	542	84%	258	88%	0.074	1.000	---
	rural	104	16%	34	12%		0.687	0.454, 1.040
DISEASE CHARACTERISTICS								
Tumor size	<=20 mm	436	67%	211	72%	0.115 *	1.000	---
	> 20 mm	204	32%	77	26%		0.780	0.572, 1.063
	missing	6	1%	4	1%		---	---
Grade	well	59	9%	43	15%	0.001	1.000	---
	moderate	169	26%	139	48%		1.129	0.718, 1.774
	poor	129	20%	57	19%		0.606	0.367, 1.001
	unknown	289	45%	53	18%		**0.252**	**0.154, 0.411**
Extent of DCIS	invasive	357	55%	133	46%	0.006	1.000	---
	invasive + DCIS	211	33%	105	36%		1.336	0.982, 1.816
	extensive DCIS	78	12%	54	18%		**1.858**	**1.246, 2.772**
LVN Invasion	no invasion	161	25%	71	24%	0.185	1.000	---
	LVN invasion	83	13%	26	9%		0.710	0.422, 1.197
	unknown	402	62%	195	67%		1.100	0.793, 1.526
ER Status	positive	409	63%	188	64%	0.030	1.000	---
	negative	137	21%	44	15%		0.699	0.477, 1.023
	missing	100	15%	60	21%		1.305	0.907, 1.878
PR Status	positive	345	53%	161	55%	0.029	1.000	---
	negative	201	31%	70	24%		0.746	0.536, 1.038
	missing	100	15%	61	21%		1.307	0.904, 1.891
Multifocality	unifocal	606	94%	259	89%	0.007	1.000	---
	multifocal	40	6%	33	11%		**1.930**	**1.190, 3.130**

*excludes missing/unknown ** bolded values are significant at 0.05

6.2 Relationship of Treatment Received to Exposure and Outcome

The relationship of treatment received to exposure (type of hospital) and outcome (survival) is summarized in Tables 10 and 11. Women initially treated at teaching hospitals were significantly more likely than their counterparts to receive BCS (72% vs. 65%) as opposed to mastectomy. They were also significantly more likely to receive radiation therapy following BCS (82% vs. 73%).

Table 10: Relationship of Treatment Received to Type of Hospital

Variable	Level	Community		Teaching		Chi-sqr	Odds	95% Confidence
		n	%	n	%	P-value	Ratio	Interval **
TREATMENT CHARACTERISTICS								
Breast conserving	no	224	35%	80	27%	**0.027**	1.000	—
surgery	yes	422	65%	212	72%		**1.407**	**1.038, 1.906**
Radiation therapy	no	112	26%	38	18%	**0.015** *	1.000	—
following BCS	yes	306	73%	173	82%		**1.666**	**1.103, 2.517**
	missing	4	1%	1	0%		—	—
Radiation therapy	no	209	93%	74	93%	0.808	1.000	—
following mastectomy	yes	15	7%	6	8%		1.130	0.423, 3.020
Chemotherapy	no	596	92%	271	93%	0.640 *	1.000	—
received	yes	50	8%	20	7%		0.880	0.514, 1.507
	missing	0	0%	1	0%		—	—
Hormone therapy	no	432	67%	221	76%	**0.014** *	1.000	—
received	yes	196	30%	67	23%		**0.668**	**0.468, 0.921**
	missing	18	3%	4	1%		—	—
Nodes sampled	1 - 9	374	57%	120	41%	**0.001**	1.000	—
	>=10	272	42%	172	59%		**1.952**	**1.469, 2.593**
Surgery only	no	428	66%	215	74%	**0.044** *	1.000	—
(no follow-up treatment)	yes	198	31%	72	25%		**0.724**	**0.528, 0.993**
	missing	20	3%	5	2%		—	—

* excludes missing/unknown ** bolded values are significant at 0.05

The difference in use of chemotherapy among those having received initial surgical treatment at a teaching hospital as compared to community hospital was not statistically significant (7% vs 8%). Women initially treated at community hospitals were, however, significantly more likely to receive hormone therapy (30% vs. 23%). Overall, women initially treated at community hospitals were more likely to undergo surgery with no subsequent therapy (31% vs 25%) and were significantly less likely to have 10 or more nodes dissected (42% vs. 59%).

The relationship of treatment received to patient outcomes is summarized in Table 11. Women receiving radiation therapy experienced significantly better survival (RR=0.51; 95%CI:0.35-0.75) than those not receiving radiation therapy, and this remained true upon controlling for type of surgery received. Type of surgery, use of chemotherapy, and use of hormone therapy were not significantly related to survival.

Women having 10 or more nodes sampled experienced significantly better survival (RR=0.61; 95%CI: 0.42-0.91) than those having fewer than 10 nodes sampled. As well, women receiving surgery without any subsequent treatment experienced significantly poorer survival than those receiving some follow-up therapy.

Table 11: Relationship of Treatment Received to Patient Outcome

Variable	Level	Frequencies		Risk	95% Confidence	Wald Stat
		n	deaths	Ratio	Interval	P-value
TREATMENT CHARACTERISTICS						
Breast conserving	no	304	44	1.000	—	
surgery	yes	634	67	0.722	0.494, 1.056	0.093
Radiation therapy	no	433	69	1.000	—	
received	yes	500	42	**0.512**	**0.349, 0.751**	**0.001**
	missing	5	-	—	—	
Chemotherapy	no	867	100	1.000	—	
received	yes	70	10	1.271	0.663, 2.435	0.470
	missing	1	1	—	—	
Hormone therapy	no	653	75	1.000	—	
received	yes	263	31	1.037	0.682, 1.576	0.866
	missing	22	5	—	—	
Nodes sampled	1 - 9	494	71	1.000	—	
	>=10	444	40	**0.614**	**0.417, 0.905**	**0.014**
Surgery only	no	578	65	1.000	—	
(no follow-up treatment)	yes	229	41	**1.536**	**1.039, 2.270**	**0.032**
	missing	20	5	—	—	

6.3 Relationship of Patient and Disease Characteristics to Treatment Received

Table 12 provides an overview of the relationships shown in Tables 7 through 11, i.e. the relationship of patient, disease, and treatment characteristics to exposure and patient outcomes. Overall, there was not an obvious relationship between women having characteristics with more favourable outcomes and type of hospital in which they received initial surgery.

Table 12: Relationship of Covariates to Exposure and Outcome

Covariate	Reference	Relationship to Exposure (hospital)	Relationship to Outcome (survival)
Patient Characteristics:			
Age at diagnosis	youngest	teaching	better
Median Family Income	highest	NS	better
Urban/rural residence	urban	NS (teaching)	NS (better)
Distance to radiation facility	closest	teaching	NS (worse)
Disease Characteristics:			
Size	smallest	NS (teaching)	better
Grade	well differentiated	NS (teaching)	better
	missing	community	NS (worse)
Estrogen receptor status	positive	NS (teaching)	better
	missing	NS (teaching)	NS (better)
Progesterone receptor status	positive	NS (teaching)	better
	missing	NS (teaching)	NS (better)
Multifocality	multifocal	teaching	NS (better)
Extent of DCIS	extensive DCIS	teaching	NS (better)
Lymph, Vascular, or Neural Invasion	LVN invasion	NS (community)	NS (worse)
	missing	NS	NS (better)
Treatment Characteristics:			
Surgery type	BCS	teaching	NS (better)
Radiation therapy	yes	teaching	better
Chemotherapy	yes	NS	NS (worse)
Hormone therapy	yes	community	NS
Nodes examined	greater	teaching	better
Surgery only	yes	community	worse

NS = not significant at 0.05

As shown previously, women initially treated at teaching hospitals were more likely to receive BCS and RT but were less likely to subsequently receive HT. Table 13 shows the proportion of women receiving BCS, RT, CT, and HT by age group, hospital type and tumour size. The association between RT, CT and HT by age group, hospital type and type of surgery is shown in Table 14.

As compared to community hospitals, women initially treated at teaching hospitals were more likely to undergo BCS for small tumours regardless of age group. Also among those with smaller tumours, there was a pattern of increased use of BCS with increasing patient age at both community and teaching hospitals.

In comparing patterns of RT use, a higher proportion of women receiving initial surgery at teaching hospitals subsequently received RT, regardless of age group. Women age 65 or older were less likely to receive RT, as were women with larger tumours. Among those initially treated at both community and teaching hospitals, subsequent use of CT was largely restricted to women under the age of 50 and among these women, those with larger tumours were more likely to receive CT.

Table 13: Proportions of Women Treated with BCS, RT, CT, and HT by Tumour Size, Type of Hospital, and Age Group

Age	Community Hospital					Teaching Hospital				
Group	% BCS	% RT	% CT	% HT	Total (n)	% BCS	%RT	% CT	%HT	Total (n)
Tumour Size < 20mm										
< 50	65% (55)	51% (43)	17% (14)	16% (13)	84	77% (44)	72% (41)	14% (8)	14% (8)	57
50-65	75% (135)	65% (115)	4% (7)	33% (58)	180	80% (67)	73% (61)	1% (1)	21% (17)	84
65-90	73% (126)	43% (74)	1% (1)	33% (55)	172	86% (60)	61% (43)	0% (0)	23% (16)	70
Total	72% (316)	53% (232)	5% (22)	30% (136)	436	81% (171)	69% (145)	4% (9)	20% (41)	211
Tumour Size >= 20mm										
< 50	60% (36)	64% (38)	40% (24)	23% (13)	60	44% (12)	52% (14)	33% (9)	33% (9)	27
50-65	49% (34)	41% (28)	4% (3)	49% (32)	69	52% (12)	43% (10)	4% (1)	35% (8)	23
65-90	43% (32)	27% (20)	0% (0)	33% (25)	75	59% (16)	33% (9)	0% (0)	28% (7)	27
Total	50% (102)	42% (86)	13% (27)	36% (70)	204	51% (40)	43% (33)	13% (10)	32% (24)	77

*excludes 10 cases for which tumour size was not reported

Table 14: Proportions of Women Treated with RT, CT, and HT by Type of Surgery, Type of Hospital, and Age Group

Age	Community Hospital				Teaching Hospital			
Group	% RT	% CT	% HT	Total (n)	%RT	% CT	%HT	Total (n)
Among women receiving BCS								
< 50	84% (78)	24% (23)	17% (16)	94	91% (51)	14% (8)	18% (10)	56
50-65	83% (138)	4% (7)	41% (67)	169	90% (71)	1% (1)	21% (16)	80
65-90	57% (90)	1% (1)	34% (53)	159	67% (51)	0% (0)	24% (18)	76
Total	73% (306)	7% (31)	32% (136)	422	82% (173)	4% (9)	21% (44)	211
Among women receiving mastectomy								
< 50	11% (6)	29% (16)	19% (10)	55	14% (4)	34% (10)	24% (7)	29
50-65	6% (5)	4% (3)	30% (23)	80	3% (1)	3% (1)	34% (10)	29
65-90	5% (4)	0% (0)	31% (27)	89	5% (1)	0% (0)	29% (6)	22
Total	7% (15)	8% (19)	27% (60)	224	8% (6)	14% (11)	29% (23)	80

6.4 Analysis of Deaths From All Causes

Among the 938 women in the cohort, a total of 111 deaths occurred on or prior to December 31, 1996. Ninety one percent of teaching hospital cases were censored as compared to 87% of community hospital cases. As shown in the table below, the follow-up times were very similar.

Table 15: Summary Statistics for Survival Times
by Type of Hospital, Deaths From All Causes

	Community Hospitals	Teaching Hospitals	Total
Number of deaths	85 (13%)	26 (9%)	111 (12%)
Number censored	561 (87%)	266 (91%)	827 (88%)
Survival Time (years):			
Mean	5.19	5.27	5.21
Median	5.41	5.41	5.41
Minimum	0.58	0.61	0.58
Maximum	6	6	6

6.4.1 Building the Model

Due to the number of potential confounders, patient, disease and treatment variables, as shown in the previous sections, were modelled in three separate analyses in order to identify those which were independent predictors of survival. Among the patient characteristics, age (<50 and 50-65) and income group were found to be independent predictors of survival (α=0.10). Among the disease characteristics, tumour size, ER and PR status were significant (α=0.10) and among the treatment characteristics, RT and number of nodes dissected were significant (α=0.10). Having received CT or HT was not significantly related to survival.

These eight terms and the primary exposure variable (hospital type) were then analysed in combination. Hospital type was not significant (RR=0.87; p=0.546). All other variables

remained significant at α =0.10 and all except PR status were significant at α =0.05.

Testing Interaction Terms

Interactions between hospital type and each of the eight terms in the model were tested for significance. Each of the disease and treatment variables in the model are related to process of care or extent of disease and could result in an effect modification. Similarly, patient characteristics may be tied to process of care. The only significant interaction was that of hospital and tumour size (p=0.027) which resulted in a significant risk ratio for hospital type.

Table 16: Results of Multivariate Analysis (α =0.10) with the Interaction Term

Variable	Parameter Estimate	Standard Error	Wald P-value	Risk Ratio	95% CI
(n=923, events=111)					
Hospital Type					
Community	--	--	--	1.00	--
Teaching	-0.6972	0.3668	0.0574	0.50	(0.24, 1.02)
Age at Diagnosis					
< 50	-0.8240	0.2686	0.0022	0.44	(0.26, 0.74)
50-65	-0.8828	0.2314	0.0001	0.41	(0.26, 0.65)
65-90	--	--	--	1.00	--
Median Family Income					
< 45,000	--	--	--	1.00	--
>= 45,000	-0.3735	0.1971	0.0581	0.69	(0.47, 1.01)
Tumour Size					
<= 20 mm	--	--	--	1.00	--
> 20 mm	0.4368	0.2225	0.0497	1.55	(1.00, 2.39)
ER Status					
positive/missing	--	--	--	1.00	--
negative	0.7851	0.2897	0.0067	2.19	(1.24, 3.87)
PR Status					
positive/missing	--	--	--	1.00	--
negative	0.4780	0.2729	0.0799	1.61	(0.95, 2.75)
Number of Nodes Examined					
< 10 nodes	--	--	--	1.00	--
>= 10 nodes	-0.4151	0.2011	0.0389	0.66	(0.45, 0.98)
Radiation therapy					
not received	--	--	--	1.00	--
received	-0.4088	0.2043	0.0454	0.66	(0.45, 0.99)
Hospital * Tumour Size	1.0384	0.4701	0.0272	2.83	(1.12, 7.10)

Reducing to the Final Model

Manual backward stepwise regression was used to reduce the model from those terms significant at α=0.10 to only those significant at α=0.05. The resulting model is shown in Table 17. Median income group, PR status, and number of nodes dissected were removed as a result.

Removal of the three variables resulted in a more significant and more precise estimate of the effect of hospital type on survival. The effect of hospital type became slightly larger as compared to that in the previous model. Overall, the level of significance for each of the remaining variables did not change. The effect of younger age and estrogen receptor status become greater in magnitude and slightly more significant. Removal of median family income changed the effect of hospital type on survival only slightly.

Table 17: Results of Multivariate Analysis (α=0.05) with the Interaction Term

Variable	Parameter Estimate	Standard Error	Wald P-value	Risk Ratio	95% CI
(n=923, events=111)					
Hospital Type					
Community	--	--	--	1.00	--
Teaching	-0.75608	0.36592	0.0388	0.47	(0.22, 0.96)
Age at Diagnosis					
< 50	-0.93846	0.26518	0.0004	0.39	(0.23, 0.66)
50-65	-0.85463	0.22992	0.0002	0.43	(0.27, 0.67)
65-90	--	--	--	1.00	--
Tumour Size					
<= 20 mm	--	--	--	1.00	--
> 20 mm	0.44164	0.22222	0.0469	1.56	(1.01, 2.40)
ER Status					
positive/missing	--	--	--	1.00	--
negative	1.14910	0.20606	0.0001	3.16	(2.11, 4.73)
Radiation therapy					
not received	--	--	--		--
received	-0.45481	0.20357	0.0255	0.64	(0.43, 0.95)
Hospital * Tumour Size	1.03694	0.46908	0.0271	2.82	(1.13, 7.07)

6.4.2 Investigating the Effect of Treatment on Survival by Hospital Type

To determine if the difference in survival by hospital type, or the effect of the interaction between hospital and tumour size, could be attributed to treatment received following surgery, treatment variables (RT, CT, and HT) were reintroduced into the model, individually and collectively. The effect on the interaction term and the primary exposure variable is shown in Table 18. The risk estimates and level of significance for hospital, tumour size, and the hospital and tumour size interaction did not vary greatly with the removal or introduction of treatment variables.

Table 18: Effect of Treatment Variables in Presence of the Hospital and Tumour Size Interaction

Variable		No Treatment Variables		RT only		HT only		CT only		RT and HT		RT and CT	
		RR	P-value	RR	P-value	RR	P-value	RR	P-value	RR	P-value	RR	P-value
Hospital Type	Community	1.00	--	1.00	--	1.00	--	1.00	--	1.00	--	1.00	--
	Teaching	0.43	0.0210	0.47	0.0390	0.43	0.0210	0.39	0.0150	0.42	0.0260	0.47	0.0400
Age at Diagnosis	< 50	0.35	0.0001	0.39	0.0004	0.36	0.0005	0.37	0.0002	0.41	0.0008	0.39	0.0014
	50-65	0.39	0.0001	0.43	0.0002	0.39	0.0001	0.37	0.0001	0.40	0.0001	0.43	0.0003
	65-90	1.00	--	1.00	--	1.00	--	1.00	--	1.00	--	1.00	--
Tumour Size	<= 20 mm	1.00	--	1.00	--	1.00	--	1.00	--	1.00	--	1.00	--
	> 20 mm	1.63	0.0270	1.56	0.0469	1.63	0.0283	1.66	0.0255	1.59	0.0400	1.55	0.0494
ER Status	positive/missing	1.00	--	1.00	--	1.00	--	1.00	--	1.00	--	1.00	--
	negative	3.06	0.0001	3.16	0.0001	3.08	0.0001	2.94	0.0001	3.02	0.0001	3.17	0.0001
Radiotherapy	received	--	--	0.64	0.0255	--	--	--	--	0.68	0.0589	0.64	0.0276
	not received	--	--	1.00	--	--	--	--	--	1.00	--	1.00	--
Hormone Therapy	received	--	--	--	--	1.12	0.6247	--	--	1.11	0.6418	--	--
	not received	--	--	--	--	1.00	--	--	--	1.00	--	--	--
Chemotherapy	received	--	--	--	--	--	--	1.02	0.9523	--	--	1.08	0.8420
	not received	--	--	--	--	--	--	1.00	--	--	--	1.00	--
Hospital * Tumour Size		3.15	0.0141	2.82	0.0271	2.97	0.0208	3.34	0.0133	3.04	0.0229	2.65	0.0393

6.4.3 Stratified Analysis

The analysis was rerun, following steps similar to that outlined previously, for only those cases with tumours less than 20mm to determine if there were additional explanatory factors within this group. The results of this analysis are shown in Table 19. Analysis of cases with tumours greater than 20mm is also shown but the number of cases was small (n=281). Among those with small tumours PR receptor status surfaced as an additional factor but the effect of hospital type on survival remained significant and was of similar magnitude to that observed previously.

Table 19: Results of Analysis Stratified by Tumour Size

Variable		Parameter Estimate	Standard Error	Wald P-value	Risk Ratio	95% CI
Tumour size ~20mm (n=644, events=57):						
Hospital Type						
	Community	--	--	--	1.00	--
	Teaching	-0.76927	0.36713	0.0361	0.46	(0.23, 0.95)
ER Status						
	positive/missing	--	--	--	1.00	--
	negative	0.77953	0.34630	0.0244	2.18	(1.11, 4.30)
PR Status						
	positive/missing	--	--	--	1.00	--
	negative	0.68207	0.33271	0.0404	1.98	(1.03, 3.80)
Radiation therapy						
	not received	--	--	--	1.00	--
	received	-0.56778	0.27071	0.0360	0.57	(0.33, 0.96)
Tumour size >20mm (n=281, events=54):						
Hospital Type						
	Community	--	--	--	1.00	--
	Teaching	0.34920	0.29724	0.2401	1.42	(0.79,2.54)
Age Group						
	< 50	-1.24700	0.36637	0.0007	0.29	(0.14,0.59)
	50-65	-1.43915	0.37308	0.0001	0.24	(0.11,0.49)
	65-90	--	--	--	1.00	--
ER Status						
	positive/missing	--	--	--	1.00	--
	negative	0.93019	0.30187	0.0021	2.53	(1.40,4.58)
Nodes Examined						
	< 10 nodes	--	--	--	1.00	--
	≥ 10 nodes	-0.57224	0.29392	0.0515	0.56	(0.31,1.00)

The results with respect to differences in survival by hospital type are consistent with those found previously. Receiving initial surgery at a teaching hospital provided a survival advantage among women with tumours less than 20mm (RR=0.46; 95%CI:0.23-0.95) but was not significant among those with larger tumours (RR=1.42; 95%CI:0.79-2.54). The effect of age on survival among those with small tumours was not significant. The effect of age among those with larger tumours was significant and greater in magnitude than was observed for those with smaller tumours (RR=0.297 vs. 0.250). The effect of ER status was significant and of similar magnitude for both small and large tumours. The effect of RT on survival was significant for those with small but not large tumours. RT had a greater effect among those with small tumours (RR=0.57; 95%CI:0.33-0.96) as compared to their counterparts (RR=0.75; 95%CI:0.41-1.37). Among those with large tumours, number of nodes examined was also significantly related to survival (p=0.051).

6.4.4 Summary

The presence of a significant interaction between hospital type and tumour size indicates that the effect of hospital on survival was different for large as compared to small tumours. Among women with small node-negative tumours, being initially treated at a teaching hospital reduced the risk of death by 53% (RR= 0.47; 95%CI:0.23-0.96), after accounting for patient and disease characteristics and treatment received. Among women with large node-negative tumours, however, being initially treated at a teaching hospital did not result in a survival advantage (RR= 1.32; 95%CI:0.73-2.32). The difference in survival is not accounted for by the type of treatments received following surgery.

Table 20: Summary of Analysis of Deaths From All Causes

	Small Tumours <= 2.0cm		Large Tumours >2.0cm	
Number of Cases				
Community Hospital	436		204	
Teaching Hospital	211		77	
Crude 5-year Survival				
Community Hospital	90.6%		84.3%	
Teaching Hospital	95.7%		83.1%	
Adjusted Risk Ratio				
Community Hospital	1.00	---	1.56	(1.01 , 2.40)
Teaching Hospital	0.47	(0.23 , 0.96)	2.06	(0.82 , 5.36)
Stratified Analysis - Adjusted Risk Ratio				
Community Hospital	1.00	---	---	
Teaching Hospital	0.46	(0.23 , 0.95)	---	

Table 21 shows the proportion of variance explained by initial treating hospital, patient characteristics, disease characteristics, and treatment received. The largest portion of

explainable variation was accounted for by disease characteristics. These characteristics provide an indication of the extent of disease as well as an indication of response to therapy. Initial treating hospital accounted for close to 5% to the total explained variance.

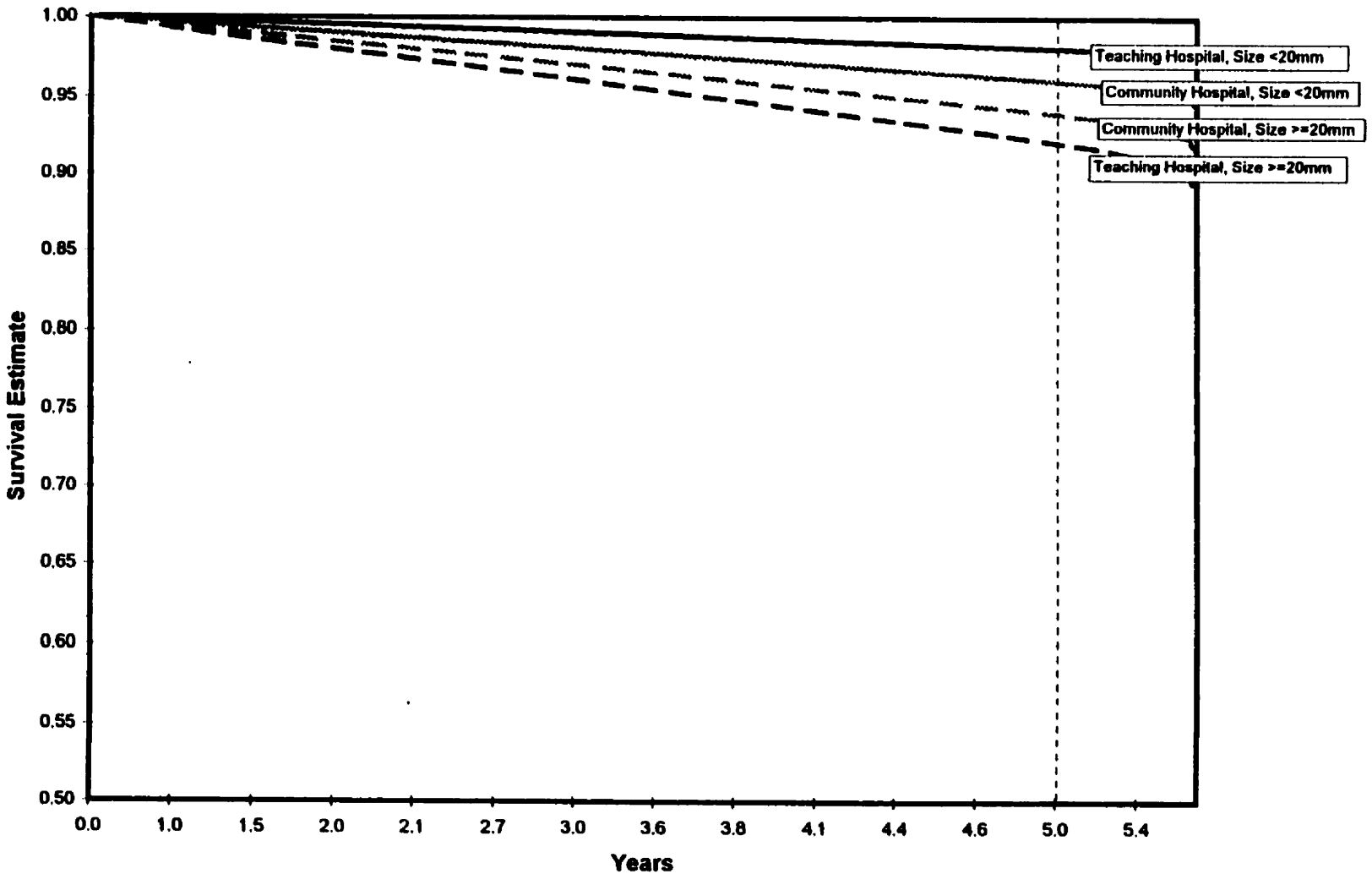
Table 21: Percent of Variance Explained by Patient, Disease, and Treatment Variables

Model (Covariates)	-2logLikelihood	Percent of Explained Variance
No covariates	1484.618	—
Final model: all covariates	1409.649	—
Difference in Log Likelihoods	74.969	100%
Initial Treating Hospital	3.520	4.7%
Patient characteristics: patient age	14.438	19.3%
Disease characteristics: tumour size, ER status	51.891	69.2%
Treatment characteristics: radiation therapy	5.12	6.8%

The following two figures show adjusted survival curves by tumour size and teaching status of the initial treating hospital. The figures represent expected survival for a hypothetical cohort of women with selected characteristics as indicated on each chart. Point estimates and 95% confidence intervals at 1, 2, 3, 4 and 5 years are provided in Appendix D.

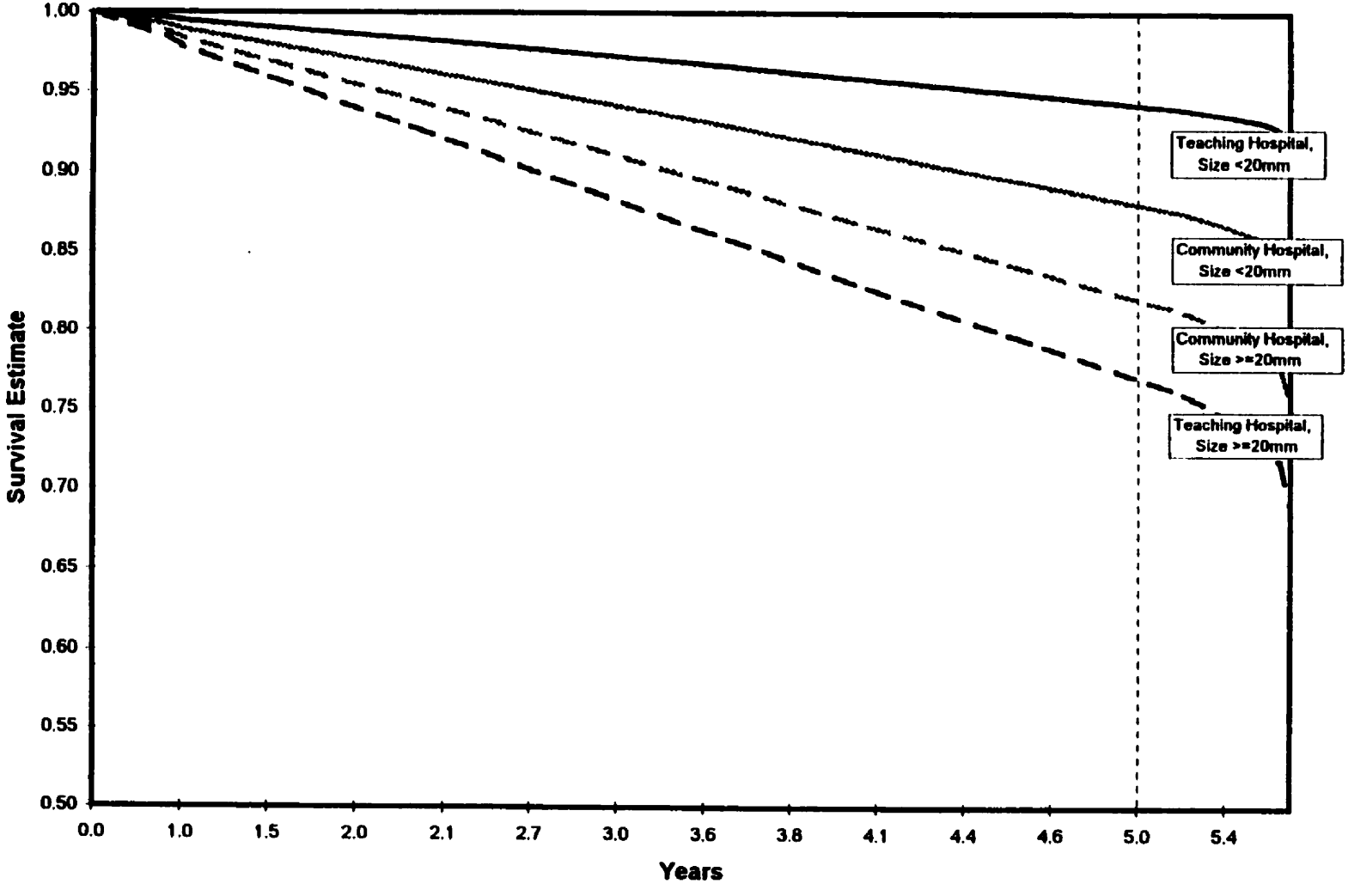
Adjusted Survival Curves by Hospital Type and Tumour Size

Age 50-65, RT received, ER positive/missing



Adjusted Survival Curves by Hospital Type and Tumour Size

Age 50-65, RT received, ER negative



6.5 Analysis of Deaths Due to Breast Cancer

Following review of death certificates, a total of 70 deaths could be classified as due to breast cancer (see Section 6.6). There were 15 deaths due to cancer among those initially treated at teaching hospitals and 55 among those initially treated at community hospitals. The power to detect a difference in survival is small. Table 22 shows the mean, median, maximum and minimum survival times by hospital. Table 23 shows the distribution of deaths due to cancer and deaths due to other causes by age group. As would be expected, the majority of deaths due to other causes occurred among women in the oldest age group.

Table 22: Summary Statistics for Survival Times by Type of Hospital, Deaths Due to Breast Cancer

	Community Hospitals	Teaching Hospitals	Total
Number of deaths	55 (9%)	15 (5%)	70 (7%)
Number censored	591 (91%)	277 (95%)	868 (93%)
Survival Time:			
Mean	5.19	5.27	5.21
Median	5.41	5.40	5.41
Minimum	0.57	0.61	0.58
Maximum	6.00	6.00	6.00

Table 23: Number and Proportion of Deaths Due to Cancer and to Other Causes by Age Group

Cause of Death Classification	Age Group		
	< 50	50 to 65	≥ 65
Deaths Due to Breast Cancer	18 (26%)	24 (34%)	28 (40%)
Deaths Due to Other Causes	3 (7%)	6 (15%)	32 (78%)
Total	21 (19%)	30 (27%)	60 (54%)

Product-Limit Estimates

Crude 5-year survival estimates (see Table 24) by hospital type show a 2.8% difference in breast cancer survival that is not significant (p=0.069). When stratified by tumour size, the difference in survival was 3.2% (p=0.068) among those with small tumours (<=20mm); there was little difference in survival (0.7%) among those with large tumours (>20mm).

Table 24: Crude Five-Year Survival Estimates by Type of Hospital, Age, Median Income, Tumour Size, and Estrogen Receptor Status, Deaths Due to Breast Cancer

Stratification Variable	Five-Year Survival (Product-Limit Estimates)			Log Rank P-value
	Community	Teaching	Difference	
Hospital Type	92.0%	94.8%	2.8%	0.0686
Age at Diagnosis:				
< 50	91.9%	94.1%	2.3%	0.4191
50 - 65	93.5%	93.6%	0.1%	0.8793
65 - 90	90.4%	96.8%	6.4%	0.0351
Median Family Income:				
< 45,000	92.1%	94.1%	2.1%	0.2561
>=45,000	91.8%	95.5%	3.7%	0.1442
Tumour Size:				
<=20 mm	93.5%	96.7%	3.2%	0.0683
> 20 mm	88.4%	89.1%	0.7%	0.6685
Estrogen Receptor Status:				
positive/missing	94.0%	97.5%	3.5%	0.0219
negative	84.4%	79.4%	-4.9%	0.5505

Multivariate Analysis

An analysis of deaths due to cancer was carried out using steps similar to that used for analysis of deaths due to all causes. In modelling patient, disease and treatment characteristics separately, tumour size, LVN invasion, grade, ER status, PR status and CT were significant at α=0.10. None of the patient characteristics were significant.

When these six variables were modelled in combination with hospital type, tumour size, LVN invasion and ER status remained significant (α=0.05). Hospital type was not significant. Interactions between hospital type and the other variables in the model were tested but none were significant.

Table 25: Results of Multivariate Analysis, Deaths Due to Breast Cancer

Variable	Parameter Estimate	Standard Error	Wald P-value	Risk Ratio	95% CI
Hospital Type					
Community	--	--	--	1.00	--
Teaching	-0.3016	0.2958	0.3079	0.74	(0.41, 1.32)
Tumour Size					
<= 20 mm	--	--	--	1.00	--
> 20 mm	0.5454	0.2435	0.0251	1.73	(1.07, 2.78)
LVN Invasion					
absent/missing	--	--	--	1.00	--
present	0.6735	0.2877	0.0192	1.96	(1.12, 3.45)
ER Status					
positive/missing	--	--	--	1.00	--
negative	1.2236	0.2447	0.0001	3.40	(2.10, 5.49)

6.6 Results of Death Certificate Review

As a result of death certificate review, cause of death information was obtained for all 19 cases for which it was not available through the OCR; however, thirteen of these cases could not be classified with certainty based on information provided on the death certificate. Of the remainder, one could be classified as a death attributable to breast cancer and five as deaths attributable to other causes. Results of this review are presented in the following table.

Table 26: Cause of Death Classification Before and After Death Certificate Review

Classification as on Vital Statistics Tape (obtained via CCO)	Classification as a Result of Death Certificate Review			Total
	Breast Cancer Death	Non-Breast Cancer Death	Equivocal	
Breast Cancer Death	64	0	0	64
Non-Breast Cancer Death	5	4	13	22
Missing	1	5	13	19
Total	70	9	26	105

*excludes 6 cases for which death certificate number was not available

All of the 64 cases which were initially attributed to breast cancer were confirmed as such. Of the 22 attributed to other causes, 5 were reclassified as breast cancer deaths and 13 could not be classified based on the information available from the death certificate. Twenty eight (27%) of the death certificates reviewed had no mention of cancer as either a cause of death or a significant condition. Date of death provided by OCR agreed with that recorded on the death certificate for all cases.

Cohen's Kappa was used to assess agreement beyond chance. Since the data being compared have essentially come from the same source, Kappa here provides a measure of completeness

rather than a measure of reliability. Considering only those cases which could be classified by either source as a death due to cancer or not (see below), Kappa was 0.58.

	Breast Cancer	Other Causes	Total	
Breast Cancer	64	0	64	Observed =0.93
Other Causes	5	4	9	Expected =0.84
Total	69	4	73	Kappa = 0.58

The same measure calculated for whether the case could be classified at all (n=105) was 0.46.

	Classified	Equivocal	Total	
Classified	73	13	86	Observed =0.82
Equivocal	6	13	19	Expected =0.66
Total	79	26	105	Kappa = 0.46

CHAPTER 7: DISCUSSION

7.1 Summary of Key Findings

The primary objective of this study was to compare the 5-year overall survival of women undergoing surgical treatment at teaching hospitals with that of women receiving surgical treatment at community hospitals (non-teaching hospitals). Results of multivariate analysis indicate that there is a significant difference in survival among women diagnosed with tumours 20mm or less in diameter. After accounting for differences in patient and disease characteristics and treatment received, women initially treated at teaching hospitals experienced a 53% reduction in relative risk of death as compared to those initially treated at community hospitals. Among women with tumours greater than 20mm at diagnosis, there was a 32% increased risk of mortality among those initially treated at teaching hospitals but this difference was not statistically significant.

The power to detect a difference in cancer survival was small due to the small numbers of deaths which could be attributed to breast cancer. The model for deaths due to breast cancer did not show a difference in survival.

7.2 Objective 1: Descriptive Statistics

Similar to that found in other studies looking at treatment of breast cancer by provider, women receiving initial surgical treatment at teaching hospitals were younger than those receiving initial surgical treatment at community hospitals (Lee-Feldstein *et al.*, 1994; Basnett *et al.*, 1992; Karjalainen, 1990; Sainsbury *et al.*, 1995) but the two groups were similar in terms of distribution by socioeconomic status (Sainsbury *et al.*, 1995; Gillis and Hole, 1996). Women treated at teaching hospitals were also more likely to live in close proximity to a facility providing radiation therapy.

With respect to tumour characteristics, the two populations did not differ significantly in terms of tumour size, which is similar to that reported in other studies (Gillis and Hole, 1996; Lee-Feldstein *et al.*, 1994). The two populations did differ significantly in terms of multifocality and extent of DCIS. Women with multifocal tumours or extensive DCIS components reported were almost twice as likely as women without these attributes reported to be treated at a teaching hospital. It is difficult to know if this is due to differences in pathology reporting or extent of tissue sampling or if, as a result of screening or biopsy, women with these characteristics were refered to or sought treatment at a teaching hospital.

Women treated at teaching hospitals were more likely to have hormone receptors reported to be positive and tumours reported to be well or moderately differentiated, although the difference was not significant. Values for tumour grade and LVN invasion were more likely to be missing for women treated at community hospitals but hormone receptor status was more likely to be

missing for women treated at teaching hospitals. Previous studies have generally found data on tumour characteristics to be missing less often at teaching hospitals and specialized centres (Gillis and Hole, 1996; Sainsbury *et al.*, 1995; Raabe *et al.*, 1997).

As has been shown fairly consistently in the literature, women undergoing surgery at teaching hospitals were significantly more likely to receive breast conserving surgery and to subsequently receive radiation therapy than were their counterparts (Basnett *et al.*,1992; Sainsbury *et al.*, 1995; Lee-Feldstein *et al.*, 1994; Satariano *et al.*, 1992; GIVIO, 1988; Nattinger *et al.*, 1992). The magnitude of these differences (OR=1.4 and 1.6 respectively) are also similar to those reported in other studies.

Women undergoing surgery at community hospitals were more likely to subsequently receive hormone therapy but there was no difference in use of chemotherapy. Previous studies have reported conflicting findings with respect to use of chemotherapy and hormone therapy among women treated at teaching hospitals or specialized centres. Women receiving surgery at community hospitals were more likely to receive surgery with no subsequent therapy, which also has been previously reported (Sainsbury *et al.*, 1995).

As well, there was a significant difference in the number of axillary lymph nodes examined. As compared to community hospitals, teaching hospitals were twice as likely to examine ten or more nodes. This relationship has been reported in some (Gillis and Hole, 1996; Raabe *et al.*, 1997) but not all (GIVIO, 1988) studies looking at breast cancer treatment in relation to teaching

status or specialization. Further reference to these findings will be made in the following sections.

7.3 Objective 2: Survival Analysis

With respect to differences in survival by treatment setting, results of this study are consistent with four of six other studies which have also looked at the effect of treatment setting or specialization on survival of women with breast cancer. Of the four studies which found a significant difference, two (Karjalainen, 1990; Basnett *et al.*, 1992) looked at the effect of teaching status and two (Sainsbury *et al.*,1995; Gillis and Hole, 1996) at the effect of specialization, as defined by the surgeon's caseload and by surgeon's specialist interest in breast cancer.

In comparison with these same studies, this study differs in that the risk reduction (53%) was restricted to women with small tumours. Basnett *et al.* detected a risk reduction of 43% among those seen at teaching hospitals. The median follow-up for this study was, however, less than three years. Both Sainsbury *et al.* and Gillis and Hole, both using a measure of surgeon's specialization and both conducted in Britain, detected risk reductions in the range of 15% to 18%. Summary statistics are not available from Karjalainen, who used standardized differences to assess differences in survival. The analysis was stratified according to local and regional disease. Among women with local disease, differences in survival by district could be accounted for by random variation. Among those with regional disease there was greater

variation, with women resident in teaching hospital districts experiencing better survival.

Of the other two studies, Lee-Feldstein and colleagues found a significantly reduced risk (26%) among women initially treated at large community hospitals but not among those initially treated at teaching hospitals, as compared to small hospitals. Bonnet *et al.* found no significant difference in survival among women treated at large public or large private hospitals as compared to small hospitals, upon controlling for patient case-mix. In comparing relative survival of women diagnosed at large public, large private, and small hospitals, Bonnet *et al.* found relative survival to be significantly better at large private hospitals as compared to large public hospitals. Neither was significant when compared to small hospitals. Multivariate analysis, however, found no significant difference in deaths due to cancer at the large public or private hospitals as compared to small hospitals. The difference in results of these two studies might be explained by differences in the population being studied.

All of these six studies looked at cohorts of women who were diagnosed and treated over a six to eleven year period prior to 1990, and thus over a period of time when mammography was being phased in and surgical management and use of systemic therapy in women with node-negative breast cancer was being reassessed. Three of the studies had available information on type of surgery and use of RT and two on use of systemic therapy. All detected a greater change over time in use of treatments at teaching hospitals and among surgeons with greater caseloads.

An interaction of tumour size with the primary exposure was not detected in any of these

studies, and it is not known if the interaction was tested for in five of the six studies. Lee-Feldstein *et al.* note that all interactions were tested and not significant. If an interaction were present, two of the studies (Karjalainen and Sainsbury) would not have been able to detect it because information on tumour size or stage was not available.

If the difference in effect by tumour size is real and present in other settings, we would expect that studies looking at survival differences among a cohort comprised mostly of women with large tumours would likely not find a significant difference without this interaction. Similarly, in a cohort consisting mostly of women with small tumours, a significant effect would more likely be observed. How this effect modification would present itself in studies classifying tumours by stage rather than size and lymph node status, is difficult to say since Stage II classification includes both large node-negative and small node-positive tumours.

Within our cohort, there was a significant difference in survival by RT which is difficult to explain. A similar observation has been reported in other cohort studies (Lee-Feldstein *et al.*, 1994). There are at least three possible explanations for this finding. While clinical trials have shown that, overall, RT does not significantly affect survival outcomes, there may be subsets of women for whom RT does significantly affect survival (Rutqvist, 1996). A second explanation may be that what is being observed is a reflection of patient or disease characteristics which were not controlled for in the analysis. A third explanation is that having received RT may be a surrogate for having received treatment at a Cancer Centre, which could affect the patient's subsequent course of treatment.

Table 27: Prognostic and Treatment Factors Considered in Published Studies Looking at Survival by Treatment Setting

Publication	Basnett *et al.* (1992)	Bonett *et al.* (1991)	Gillis & Hole (1996)	Karjalainen (1990)	Lee-Feldstein *et al.* (1994)	Sainsbury *et al.* (1995)
STUDY YEARS	1982-86	1980-86	1980-88	1970-81	1984-90	1979-88
COUNTRY	England	Australia	Scotland	Finland	U.S.	England
PROGNOSTIC FACTORS						
Age at diagnosis	< 50 50-74	< 40 40-54 55-69 70+	< 50 50-64 65-74	✓ (relative rates and indirect standardization)	< 30 30-49 50-69 70+	< 50 50-64 65-79 80+
Tumor size (cm)		0 -2.0 2.0-3.0 ≥ 3.0	< 2.0 2.0-3.9 ≥ 4.0		< 1.0 1.1-2.0 2.1-4.0 > 4.0	
Lymph node involvement		✓	✓		✓	✓
Stage	✓			✓ (stratified by localized or regional disease)	✓ (stratified by localized or regional disease)	
Tumor grade			✓			✓
ER status						
PR status						
Histology					✓	
Socio-economic status		✓	✓			✓
Period of diagnosis	✓				✓	✓
TREATMENT FACTORS						
Type of surgery	✓				✓	✓
Radiation therapy	✓				✓	✓
Chemotherapy	✓					✓
Hormone therapy	✓					✓
FINDINGS	significantly reduced risk among those treated at teaching hospitals	No difference in survival at large private or public hospitals as compared to small hospitals	Significantly reduced risk among those treated by specialist surgeons	Relative survival was better for those living in university hospital districts	Significantly better survival at large hospitals but not at teaching hospitals as compared to small hospitals	Significantly better survival among those treated by surgeons with greater caseloads

7.4 Interpretation of Findings

There are a number of possible explanations for the findings of this study. Survival differences by hospital type may be reflection of: residual confounding arising from factors not controlled for in the analysis, an artifact arising from misclassification of cases with respect to disease stage, or differences in care received. Confounding would come into play if the two patient populations differed in terms of prognostic factors which were not controlled for in the analysis. We would expect this difference to be apparent by tumour size as well as by hospital type, since the survival advantage was apparent only among those with smaller tumours.

An example of this would be differences in the proportion of women screened via mammography and subsequently treated at teaching as compared to community hospitals. This could result if those physicians who are most likely to recommend mammographic screening are also most likely to refer patients to teaching hospitals. The difference in survival could be due to lead time bias, ie. the tumour being detected earlier rather than an actual increase in survival resulting from interventions, or to differences in the type of tumours being detected. Screen detected tumours are likely to be less aggressive with a longer pre-clinical period and may have better prognosis than those presenting clinically, irrespective of treatment administered. As well, women who attend screening may have different behaviours or attitudes with respect to health and are likely to be from higher SES groups. These biases as a result of mammography would play a bigger role in small tumours which are less likely to be symptomatic and less likely to be detected via physical exam. Tumours greater than 20mm are more likely to be symptomatic and detected by the patient.

A second explanation for the findings may be that what is being observed is an artifact due to misclassification of tumours, particularly with respect to nodal status. Lymph node status is currently considered one of the most important prognostic factors in women with breast cancer and is a factor in determining treatment. In limiting the cohort to women with confirmed node-negative tumours and controlling for other prognostic factors in the multivariate analysis, we are making the assumption that we are comparing outcomes among women with similar prognostic factors. However, there is evidence to suggest that examination of fewer nodes increases the risk of classifying a patient as node-negative when she in fact does have involved nodes. Within our cohort, teaching hospitals examined a significantly greater number of nodes as compared to community hospitals; this was true for both small and large tumours. While nodal status can also be assessed via physical exam, Fisher *et al.* found clinical assessment to have high false-positive and false-negative rates (Fisher *et al.*, 1989). From this we might expect that there is a greater chance that women treated at community hospitals were misclassified as node-negative. There is also evidence to suggest that teaching hospitals and specialized centres are more likely to do a more thorough diagnostic workup in general (Basnett *et al.*, 1992; Greenberg *et al.*, 1991). In our cohort, we observed a lower rate of missing values for important prognostic factors among women initially treated at teaching hospitals.

We would expect misclassification to occur more frequently among women with smaller tumours. Probability of metastasis, as well as lymph node involvement, increases with increasing tumour size and evidence of metastasis is less likely to be missed than nodal involvement without metastasis. As well, information on nodal status may be more likely to

influence decisions regarding use of adjuvant therapy in treatment of women with small as compared to large tumours (Haffty *et al.*, 1997).

A third explanation for the findings of this study may lie in differences in practice patterns between the hospitals. In this study, we have controlled for whether or not specific treatments were administered but within any mode of treatment there is room for variation in terms of how and to whom it is administered. A number of studies have demonstrated that this variation does in fact exist. There is also evidence to suggest that teaching hospitals and specialized centres are quicker to alter practices based on new evidence and guidelines (Sainsbury *et al.*, 1995; Lee-Feldstein *et al.*, 1994; Basnett *et al.*, 1992; Studnicki 1993) and more likely to administer appropriate care (Schleifer *et al.*, 1991; Grilli *et al.*, 1993; Hand *et al.*, 1991).

There are a number of reasons why treatment patterns may play a bigger role in the outcomes of women with small tumours. Medical interventions, particularly systemic therapy, may have a greater impact on the survival among women diagnosed with small tumours. As well, appropriate treatment of women with small node-negative tumours, particularly those at moderate risk of recurrence, is not as well established as that for women with larger tumours, who will generally be considered at high risk. Randomized trials, and meta-analyses of these trials (Early Breast Cancer Trialists' Collaborative Group, 1992; 1998), are identifying subsets of women with early breast cancer who can benefit from chemotherapy and hormone therapies, tamoxifen in particular. All of this allows room for variation in treatment based on physician and patient preferences.

7.5 Death Certificate Review

Review of death certificates was undertaken in an effort to obtain more complete information regarding cause of death. However, the quality of data was not significantly improved as a result of this review. Of the cases for which cause of death was missing, only a third could be classified as due to or not due to breast cancer based on the information obtained from the death certificate. In total, 25% of the cases could not be classified based on the data available from the death certificate.

Although Vital Statistics data are generally accepted to be reliable with respect to determining vital status, in some cases they do not provide sufficient information to accurately determine cause of death for women diagnosed with breast cancer. If breast cancer survival is to be used as an outcome other sources of information will need to be assessed.

7.6 Study Limitations

One limitation of the study lies in the short period of follow-up. It has been suggested that caution be used in analysis of survival data at five years as this may not be predictive of long-term outcomes. As well, given the method of follow-up used, it was not possible to distinguish alive cases from those lost-to-follow-up. A study looking at the validity of outcome ascertainment using Vital Statistics death registrations estimated the rate for ascertainment of deaths occurring in Ontario to be close to 98% (Schnatter *et al.*, 1990). A similar study, however, has not been done for women with breast cancer.

As well, grouping together all non-teaching hospitals, based on the 1991 Canadian Hospital Directory, may have damped the effect of treatment setting on survival since some of these hospitals may be more similar to teaching hospitals than to the smaller community hospitals. A more appropriate hospital classification may be one based on the presence of a multi-disciplinary breast program.

Data were not available for menopausal status or presence of comorbid conditions and, although data for most variables used in this study were fairly complete, grade was not available for over a third of the cases. The study had limited power for survival analysis of mortality from breast cancer. Sub-group analysis was also restricted due to the small number of cases.

In terms of generalizability of the study, the cohort excluded node-negative women treated at two facilities which refused to participate in the original study, one of which was a regional

cancer centre (272 cases) and the other a community hospital (3 cases). As well, the study cohort excluded women with node-positive tumours and those with undetermined nodal status.

7.7 Implications

A two-fold difference in survival, if it cannot be accounted for by patient differences, suggests that there is room for change in care being provided to women with node-negative breast cancer. This is particularly important since fewer than half of women diagnosed with early breast cancer were treated at teaching hospitals.

What this means for the way health care is delivered to these women depends on what is giving rise to this difference. If the difference in survival between teaching and community hospitals is attributed to differences in treatment or to misclassification with respect to disease staging, efforts need to be directed at facilitating physician and patient education. The need to promote consistent evidence-based care has been previously identified and a number of regions, including Ontario, have responded by establishing systems for development of guidelines for the treatment of women breast cancer. As there is also evidence to suggest that in the presence of clinical guidelines (Olivotto *et al.*, 1997; Schleifer *et al.*, 1991), there remains variation in the care delivered to women with breast cancer, an understanding of factors which contribute to this variation and how this relates to patient outcomes is required.

If the difference is attributed to care being received in a multidisciplinary setting or expertise

gained through specialization, knowledge which is not conveyed through evidence-based guidelines, efforts may need to be directed at facilitating consultation between physicians and between physicians and other health service providers. Centralising the treatment of women with breast cancer is likely not a feasible option simply given the volume of cases. Implementation of a regionalized system of care is being undertaken in Ontario. As well, other regions with existing practice guidelines have indicated specific situations when consultation with or referral to a specialist would be appropriate.

While the gain in survival may not appear large because of the generally good survival rate among women with node-negative breast cancer, the difference observed between treatment settings is similar to that ascribed to the use of systemic therapy. As well, there are subsets of node-negative women for whom this difference in survival could be considerable.

CHAPTER 8: FUTURE RESEARCH

This study adds to a small but growing body of literature looking at the effect of specialization and treatment setting on survival of women with breast cancer. It is the first to be done in Canada and one of the few in which data on treatments received was available but there remain many unanswered questions.

Replication of the study with greater power and longer duration of follow-up is required, as are studies which examine this relationship with respect to recurrence and disease-free survival. There is also a need to identify specific components of care which may contribute to differences in survival by treatment setting. Replication of the study in other provinces would help to shed light on factors which may or may not be contributing to this difference in survival. As well, studies are required to determine if a similar relationship exists among women with node-positive breast cancer and women for whom nodal status is undetermined.

REFERENCES

Arriagada R, Le MG, Rochard F, Contesso G. Conservative treatment versus mastectomy in early breast cancer: patterns of failure with 15 years of follow-up data. Institut Gustave-Roussy Breast Cancer Group. *J Clin Oncol* 1996; 14:1558-64.

Atkinson EN, Brown BW, Montague ED. Tumor volume, nodal status, and metastasis in breast cancer in women. *J Natl Cancer Inst* 1986; 76:171-178.

Axelsson CK, Mouridsen HT, Zedeler K. Axillary dissection of level I and II lymph nodes is important in breast cancer classification. The Danish Breast Cancer Cooperative Group (DBCG) *Eur J Cancer* 1992; 28A(8-9):1415-8.

Basnett I, Gill M, Tobias JS. Variations in breast cancer management between a teaching and non-teaching district. *Eur J Cancer* 1992; 28A: 1945-50.

Bassett MT, Kreiger N. Social class and black-white differences in breast cancer survival. *Cancer* 1990; 66: 819-826.

Blichert-Toft M, Rose C, Andersen JA, et al. Danish randomized trial comparing breast conservation therapy with mastectomy: six years of life-table analysis. *Monogr Natl Cancer Inst* 1992; 11:19-25.

Bonett A, Roder D, Esterman A. Case-survival rates for infiltrating ductal carcinomas by category of hospital at diagnosis in South Australia. *Med J Aust* 1991; 154: 695-697.

Breast Cancer Trialists' Collaborative Group. Effects of Radiotherapy and surgery in early breast cancer. An overview of the randomized trials. *N Engl J Med* 1995; 333(22): 1444-55.

British Columbia Cancer Agency. B.C. Cancer Agency: Cancer Management Manual, November 1998. Available fromURL: http:/www.bccancer.bc/ca.cmm/ (November 12, 1998).

Bryant H, Mah Z. Breast cancer screening attitudes and behaviors of rural and urban women. *Prev Med* 1992; 21(4): 405-18.

Canadian Hospital Directory 1991-1992. Ottawa: Canadian Hospital Association, 1992.

Carbone PP, Jordan VC, Bonadonna G. Neoplasms of the Breast. In: Abeloff MD (ed). Clinical Oncology. New York: Churchill Livingstone, 1995.

Carnon AG, Ssemwagerere A, Lamont DW, Hole JD, Mallon EA, George WD, Gillis CR. Relation between socioeconomic deprivation and pathological prognostic factors in women with breast cancer. BMJ 1994; 309: 1054-1057.

Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. *Cancer* 1989; 63: 181-7.

Casciato DA, Lowitz BB (eds). Manual of Clinical Oncology, Second Edition. Boston/Toronto: Little, Brown and Company, 1988.

Clark EA, Marrett LD, Kreiger N. Twenty Years of Cancer Incidence, 1964-1983: The Ontario Cancer Registry. Toronto: The Ontario Cancer Treatment and Research Foundation, 1987.

Clark RM, Whelan T, Levine M, et al. Randomized clinical trial of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer: an update. *J Natl Cancer Inst* 1996; 88: 1659-64.

Delides GS, Garas G, Georgouli G, et al. Intralaboratory variations in the grading of breast carcinoma. (Abstract) *Arch Pathol Lab Med* 1982; 106:126-8.

Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic or immune therapy. 133 randomized trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. *Lancet* 1992; 339:1-15.

Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic or immune therapy. 133 randomized trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. *Lancet* 1992; 339:71-85.

Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and surgery in early breast cancer: An overview of the randomized trials. *N Engl J Med* 1995; 333:1444-55.

Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet* 1998; 351: 1451-67.

Farley TA, Flannery JT. Late-stage diagnosis of breast cancer in women of lower socioeconomic status: Public health implications. *Am J Public Health* 1989; 79(11): 1508-12.

Farrow DC, Hunt WC, Samet JM. Geographic variation in the treatment of localized breast cancer. *N Engl J Med* 1992; 326(17):1097-101.

Feinstein AR, Sasin DM, Wells CK. The Will Rogers Phenomenon: Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *N Engl J Med* 1985; 312(25):1604-8

Fellegi IP, Sunter AB. A theory of record linkage. *J Am Stat Assoc* 1969; 64:1183-1210.

Fisher B, Redmond C, Fisher ER, Caplan R, et al. Relative worth of estrogen and progesterone receptor and pathologic characteristics of differentiation as indicators of prognosis in node negative breast cancer patients: Findings from National Surgical Adjuvant Breast and Bowel Project Protocol B-06. *J Clin Oncol* 1988; 6(7):1076-1087.

Fisher B, Anderson S, Redmond CK, Wolmark N, Wickerham DL, Cronin WM. Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med* 1995; 333(22): 1456-1461.

Fisher B, Redmond C, Dimitrov NV, et al. A randomized clinical trial evaluating sequential methotrexate and fluorouracil in the treatment of patients with node-negative breast cancer who have estrogen-receptor-negative tumors. *N Engl J Med* 1989; 320:473.

Forrest PA, Stewart HJ, Everington PA, et al. Randomized controlled trial of conservation therapy for breast cancer: 6-year analysis of the Scottish trial. *Lancet* 1996; 348:708-13.

G.I.V.I.O (Interdisciplinary Group for Cancer Care and Evaluation) Performance of general hospitals in delivering adjuvant chemotherapy to breast cancer patients. *Tumori* 1988; 74(4): 377-86.

Gilchrist KW, Kalish L, Gould VE, et al. Interobserver reproducibility of histopathological features in stage II breast cancer. *Breast Cancer Res Treat* 1985; 5: 3-10.

Gillis GR, Hole DJ. Survival outcome of care by specialist surgeons in breast cancer: a study of 3786 patients in the west of Scotland. *BMJ* 1996; 312: 145-148.

Goel V, Olivotto I, Hislop TG, Sawka C, Coldman A, Holowaty EJ. Patterns of initial management of node-negative breast cancer in two Canadian provinces. *Can Med Assoc* J 1997; 156(1): 25-35.

Grady KE, Lemkau JP, et al. The importance of physician encouragement in breast cancer screening of older women. *Preventive Med* 1992; 21(6): 766-80.

Greenberg ER, Baron JA, Dian BJ, Freeman DH, Yates JW, Korson R. Cancer staging may have different meanings in academic and community hospitals. *J Clin Epidemiol* 1991; 44(6): 505-512.

Gregory WM, Bolland K, Whithead J, Souhami RL. Cautionary tales of survival analysis: conflicting analyses from a clinical trial in breast cancer. *Br J Cancer* 1997; 76(4): 551-558.

Grilli R, Minozzi S, Tinazzi A, Labianca R, Sheldon TA, Liberati A. Do specialists do it better? The impact of specialization on the processes and outcomes of care for cancer patients. *Ann Oncol* 1998; 9: 365-374.

Haffty BG, Ward B, Pathare P, et al. Reappraisal of the role of axillary lymph node dissection in the conservative treatment of breast cancer. *J Clin Oncol* 1997; 15(2): 691-700.

Hand R, Sener S, Imperato J, et al. Hospital variables associated with quality of care for breast cancer patients. *JAMA* 1991; 266: 3429-32.

Harris JR. Staging of breast carcinoma. In: Harris JR, Hellman S, Henderson IC, Kinne DW (eds). Breast Diseases. Philadelphia: J.B. Lippincott Company, 1991.

Harris JR, Morrow M, Bonadonna G. Cancer of the Breast. In: DeVita VT, Hellman S, Rosenberg SA (eds). Cancer: Principles and Practice of Oncology, Fourth Edition. Philadelphia: J.P. Lippincott Co., 1993.

Henderson IC. Adjuvant systemic therapy of early breast cancer. In: Harris JR, Hellman S, Henderson IC, Kinne DW (eds). Breast Diseases. Philadelphia: J.B. Lippincott Company, 1991.

Holowaty EJ, Marrett LD, Fehringer G. Cancer Incidence in Ontario, Trends and Regional Variations in the 1980's. Toronto: The Ontario Cancer Treatment and Research Foundation, 1995.

Howe GR, Lindsay J. A generalized iterative record linkage computer system for use in medical follow-up studies. *Comput Biomed Res* 1981; 14: 327.

Iscoe NA, Goel V, Wu K, Fehringer G, Holowaty E, Naylor CD, Phil D. Variation in breast cancer surgery in Ontario. *Can Med Assoc J* 1994; 150(3): 345-352.

Jacobsen BL, Lund E. Level of education, use of oral contraceptives and reproductive factors: the Tromso Study. *Int J of Epidemiol* 1990; 19(4): 967-70.

Jacobson JA, Danforth DN, Cowan KH, D'Angelo T, et al. Ten-year results of a comparison of conservation with mastectomy in the treatment of stage I and II breast cancer. *N Engl J Med* 1995; 332(14): 907-911.

Karjalainen S. Geographical variation in cancer patient survival in Finland: chance, confounding, or effect of treatment? *J Epidemiol Community Health* 1990; 44: 210-4.

Karjalainen S, Pukkala E. Social class as a prognostic factor in breast cancer survival. *Cancer* 1990; 66: 819-826.

Katz SJ, Hofer TP. Socioeconomic disparities in preventive care persists despite universal coverage. Breast and cervical cancer screening in Ontario and the United States. *JAMA* 1994; 272(7): 530-4.

Keirn W, Metter G. Survival of cancer patients by economic status in a free care setting. *Cancer* 1985; 55: 1552-5.

Kogevinas M, Marmot MG, Fox AJ, Goldblatt PO. Socioeconomic differences in cancer survival. *J Epidemiol Community Health* 1991; 45: 216-219.

Koscielny S, Tubiana M, Le MG, et al. Breast cancer: relationship between the size of the primary tumour and the probability of metastatic dissemination. *Br J Cancer* 1984; 49: 709-715.

Lauver D, Coyle M, Panchamatia B. Women's reasons for and barriers to seeking care for breast cancer symptoms. *Women's Health Issues* 1995; 5(1): 27-35.

Lee-Feldstein A, Anton-Culver H, Feldstein PJ. Treatment differences and other prognostic factors related to breast cancer survival. *JAMA* 1994; 271(15): 1163-8.

Liljegren GG, Holmberg L, Adami HO, et al. Sector resection with or without postoperative radiotherapy for stage I breast cancer: five year results of a randomized trial. *J Natl Cancer Inst* 1994; 86: 717-22.

Mackillop WJ, Zhang-Salomons J, Groome P, Paszat L and Holowaty E. Socioeconomic status and cancer survival in Ontario. *J Clin Oncology* 1997; 15(4):1680-1689.

Mandelblatt J, Andrews H, Kerner J, Zauber A, Burnett W. Determinants of late stage diagnosis of breast and cervical cancer: the impact of age, race, social class, and hospital type. *Am J Public Health* 1991; 81(5): 646-9.

Mansour EG, GrayR, Shatila AH, et al. Efficacy of adjuvant chemotherapy in high-risk node-negative breast cancer. *N Engl J Med* 1989; 320:485.

McLaughlin JR, Sloan MR, Janovjak DP. Cancer Survival in Ontario. Toronto: The Ontario Cancer Treatment and Research Foundation, 1995.

Mercer SL, Goel V. Factors associated with the use of mammography: The Ontario Health Survey. *Cancer Prevention and Control* 1997; 1(2): 144.

Mirsky D, O'Brien SE, McCready D, et al. Surgical management of early stage invasive breast cancer (stage I and II). *Cancer Prevention and Control* 1997; 1(1): 10-17.

Michielutte R, Diesker RA. Racial differences in knowledge of cancer: a pilot study. *Social Science Med* 1982; 16: 245.

Mor V, Masterson-Allen S, Goldberg R, Guadagnoli E, Wool MS. Pre-diagnostic symptom recognition and help seeking among cancer patients. *J Com Health* 1990; 15(4): 253-66.

National Cancer Institute of Canada. Canadian Cancer Statistics 1997. Toronto, Canada, 1997.

National Cancer Institute of Canada. Canadian Cancer Statistics 1998. Toronto, Canada, 1998.

National Institutes of Health Consensus Conference. Treatment of early-stage breast cancer. *JAMA* 1991; 265: 391-395.

Nattinger AB, Gottlieb MX, Veum J, Yahnke D, Goodwin JS. Geographic variation in the use of breast-conserving treatement for breast cancer. *N Engl J Med* 1992; 326(17):1102-7.

Newcombe HB, Smith ME, Howe GR, Mingay J, Strugnell A, Abbatt JD. Reliability of computerized versus manual death searches in a study of the health of Eldorado uranium miners. *Comput Biol Med* 1983; 13: 157-169

Newcombe HB. Handbook of Record Linkage: Methods for Health and Statistical Studies, Administration, and Business. Oxford: Oxford University Press, 1988.

Olivotto A, Coldman AJ, Hislop TG, et al. Compliance with paactice guidelines for node-negative breast cancer. *J Clin Oncol* 1997; 15(1): 216-22.

Priestman TJ, Bullimore JA, Godden TP et al. The Royal College of Radiologists' fractionation survey. *Clin Oncol* 1989; 1: 39-46.

Provincial Breast Cancer Disease Site Group. Adjuvant systemic therapy for node-negative breast cancer (No.1-8). Ontario: Cancer Care Ontario Practice Guidelines Initiative, November 1998.

Raabe NK, Kaaresen R, Fossaa SD. Hospital-related differences in breast cancer management. *Breast Cancer Res Treatment* 1997; 43: 225-235.

Reeves MJ, Newcombe PA, Remington PL, Marcus PM. Determinants of breast cancer detection among Wisconsin (United States) women, 1988-90. *Cancer Causes Control* 1995; 6(2): 103-11.

Richardson JL, Langholz B, Bernstein L, Burciaga C, Danley K, Ross RK. Stage and delay in breast cancer diagnosis by race, socioeconomic status, age and year. *Br J Cancer* 1992; 65(6): 922-6.

Rimpela AH, Pukkala EI. Cancers of affluence: positive social class gradient and rising incidence trend in some cancer forms. *Social Science Med* 1987; 24(7): 601-6.

Roberts MM, Alexander FE, Elton RA, Rodger A. Breast cancer stage, social class and the impact of screening. *Eur J Surg Oncology* 1990; 16(1): 18-21.

Robles SC, Marrett LD, Clarke EA, Risch HA. An application of capture-recapture methods to the estimation of completeness of cancer registration. *J Clin Epidemiol* 1988; 41(5): 495-501.

Rosen PP, Groshen S, Saigo P, et al. Pathological prognostic factors in stage I (T1N0M0) and stage II (T1N1M0) breast carcinoma: a study of 644 patients with median follow-up of 18 years. *J Clin Oncol* 1989; 7: 1239-1251.

Ross NA, Rosenberg MW, Pross DC, Bass B. Contradictions in women's health care provision: a case study of attendance for breast cancer screening. *Social Science Med* 1994; 39(8): 1015-25.

Rutqvist LE. Breast Cancer. *Acta Oncol.* 1996; 35 (suppl 7): 54-63.

Sainsbury R, Haward B, Rider L, Johnston C, Round C. Influence of clinician workload and patterns of treatment on survival from breast cancer. *Lancet* 1995; 345:1265-1270.

Satariano ER, Swanson GM, Moll PP. Nonclinical factors associated with surgery received for treatment of early-stage breast cancer. *Am J Public Health* 1992; 82: 195-198.

Sawka C, Olivotto I, Coldman A, et al. The association between population-based treatment guidelines and adjuvant therapy for node-negative breast cancer. *Br J Cancer* 1997; 75(10): 1534-1542.

Sawka CA, O'Connor AM, Llewellyn-Thomas HA, *et al.* Appropriateness of adjuvant systemic therapy for axillary node-negative breast cancer: a physician opinion survey. *J Clin Oncol* 1995; 13(6): 1459-69.

Schleifer SJ, Bhardwaj S, Lebovits A, et al. Predictors of physician nonadherence to chemotherapy regimens. *Cancer* 1991; 67: 945-951.

Schnatter AR, Acquavella JF, Thompson FS, Donaleski D, Theriault G. An analysis of death ascertainment and follow-up through Statistics Canada's mortality data base system. *Can J Public Health* 1990; 81: 60-64.

Schouten LJ. Hupperets PS, Jager JJ, et al. Prognostic significance of etiological risk factors in early breast cancer. *Breast Cancer Res Treat* 1997; 43(3): 217-23.

Schrijvers CTM, Coebergh JWW, van der Heijden LH, Mackenback JP. Socioeconomic status and breast cancer survival in the Southeastern Netherlands, 1980-1989. *European J Cancer.* 1995; 31A(10):1660-1664.

Shannon HS, Jamieson E, Walsh C, Julian J, Fair M, Buffet A. Comparison of individual follow-up and computerized record linkage using the Canadian Mortality Data Base. *Can J Public Health* 1989; 80: 54-57.

Shapiro S, Venet W, Strax P, Venet L, Roeser R. Selection, follow-up, and analysis in the Health Insurance Plan Study: a randomized trial with breast cancer screening. *Natl Cancer Institute Monographs* 1985; 67:65-74.

Sivaramakrishna R, Gordon R. Detection of breast cancer at a smaller size can reduce the likelihood of metastatic spread. *Acad Radiol* 1997; 4: 8-12.

Smith ME, Newcombe H. Use of the Canadian Mortality Data Base for epidemiological follow-up. *Can J Public Health* 1982; 73: 39-46.

Sosa J, Diener-West M, Gusev Y, et al. Association between extent of axillary lymph node dissection and survival in patients with stage I breast cancer. *Ann Surg Oncol* 1998; 5(2): 140-149.

Studnicki J, Schapira DV, Bradham DD, et al. Response to the National Cancer Institute Alert. The effect of practice guidelines on two hospitals in the same medical community. *Cancer* 1993; 72: 2986-2992.

Tabar L, Fagerberg G, Duffy SW, Day NE. The Swedish two county trial of mammographic screening for breast cancer: recent results and calculation of benefit. *J Epidemiol Community Health* 1989; 43(2): 107-14.

The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Clinical practice guidelines for the care and treatment of breast cancer. *CMAJ* 1998; 158(3 suppl).

Thomas SM, Fick AC. Women's health. Part II: Individual, environmental and economic factors affecting adherence to recommended screening practices for breast cancer. *J Louisiana State Med Soc* 1995; 147(4): 149-55.

Tomatis L (ed.) Cancer, causes, occurrence, and control. Lyons: IARC Scientific Publications, 1990. (No. 100).

Tubiana M, Koscielny S. Natural history of human breast cancer: recent data and clinical implications. *Breast Cancer Res Treatment* 1991; 18(3): 125-40.

Vagero D, Persson G. Cancer survival and social class in Sweden. *J Epidemiol Commun Health* 1987; 47: 204-209.

Van Lancker M, Goor C, Sacre R, Lamote J, et al. Patterns of Axillary Lymph Node Metastasis in Breast Cancer. *Am J Clin Oncol* 1995; 18(3): 267-272.

Van Loon AJM, Burg J, Goldbohm RA, van den Brandt PA. Differences in cancer incidence and mortality among socio-economic groups. *Scand J Soc Med* 1995; 23(2): 110-120.

van Dongen JA, Bartelink H, Fentiman IS, et al. Factors influencing local relapse and survival and results of salvage treatment after breast-conserving therapy in operable breast cancer: EORTC trial 10801, breast conservation compared with mastectomy in TNM stage I and II breast cancer. *Eur J Cancer* 1992; 28A: 801-5.

Veronesi U, Luini A, Del Vecchio M, et al. Radiotherapy after breast-conserving surgery in women with localized cancer of the breast. *N Engl J Med* 1993; 328:1587-91.

Veronesi U, Banfi A, Salvadori B, et al. Breast conservation is the treatment of choice in small breast cancer: long-term results of a randomized trial. *Eur J Cancer* 1990; 26:668-70.

Wells BL, Horm JW. Stage at diagnosis in breast cancer: Race and socioeconomic factors. *Am J Public Health* 1992; 82(10): 1383-5.

Whelan TJ, Lada B, Perera FE, et al. Breast irradiation in women with early stage invasive breast cancer following breast conserving surgery. *Cancer Prevention and Control* 1997; 1(3): 228-240.

Whelan T, Marcellus D, Clark R, Levine M. Adjuvant radiotharapy for early breast cancer: patterns of practice in Ontario. *Can Med Assoc J* 1993: 149(9): 1273-1277.

Wilcox LS, Mosher WD. Factors associated with obtaining health screening among women of reproductive age. *Public Health Rep* 1993; 108(1): 76-86.

Wilkins R. Use of postal codes and analysis of health data. *Health Rep* 1993; 5: 157-177.

Wong William W, Vijaykumar S, Weichselbaum R. Prognostic indicators in node-negative early stage breast cancer. *Am J Med* 1992; 92: 539-548.

World Health Organization. Manual of the International Classification of Diseases, Injuries, and Causes of Death - Ninth (1975) Revision. Geneva: World Health Organization, 1977.

APPENDIX A

THE NODE-NEGATIVE COHORT: CODING OF VARIABLES ON THE ORIGINAL DATA FILE

Node-Negative Cohort - Original Data File

	Variable	# Missing	Coding	Distrib'n
Patient Characteristics				
age at diagnosis	DXAGE	none	range: 21 - 88	$\bar{x}$ = 60
urban/rural residence	URBAN	none	0 = rural (2nd digit = '0') 1 = urban	138 800
postal code	POSTCODE	none		
median family income	AVGMED	none		
distance to radiation facility (straight line)	DIST_RT	none	0 = 0 - 50 1 = 51-100 2 = > 100	852 69 17
Disease Characteristics				
diagnosis date	DIAGDT	none	1991	
tumour size (in mm)	SIZE	10	range 01- 90 999 = unknown, not stated	928 10
location of tumour	LOCATION	33	1 = central 2 = non-central 3 = multifocal 9 = unknown, not stated	53 779 73 33
grade	GRADE	342	1 = well 2 = moderate 3 = poor 9 = not determined, not stated	102 308 186 342
number of nodes examined	EXAMNODE	24	range: 1- 31 98 = unknown, all were negative	$\bar{x}$ =9.7 24
lymph, vascular, neural invasion	INVADE	597	0 = no invasion 1 = LVN invasion 9 = unknown	232 109 597
extent of ductal carcinoma in situ	EXTENT	none	1 = invasive 2 = invasive + DCIS 3 = in_ DCIS+	490 316 132
multifocality	MULTIFOC	none	0 = unifocal 1 = multifocal	865 73
estrogen receptor status	ER_NEW		0 = positive 1= negative 2= unknown	597 181 160

progesterone receptor status	PGR_NEW		0= positive 1= negative 2= unknown	506 271 161
Treatment Characteristics				
type of surgery received	SURGERY	none	1 = breast conserving surgery 2 = MRM (mastectomy)	634 304
extent of residual tumour	RESIDTUM	5	0 = none 1 = micro 2 = macro 3 = DCIS_mis 4 = DCIS_mac 9 = unknown	901 22 3 7 0 5
Radiation treatment summary	RT_SUMBC	5	1 = no radiation therapy 2 = radiation therapy received 3 = unknown	433 500 5
Chemotherapy summary	CHEMO_BC	1	1 = no chemotherapy 2 = chemotherapy received 3 = unknown	867 70 1
Hormone treatment summary	HORM_BC	22	1 = no hormone therapy 2 = hormone therapy received 3 = unknown	653 263 22
Hospital Characteristics				
Hospital in which surgery was performed	TYPEHOSP	none	1 = cancer centre 2 = teaching hospital 3 = community hospital	0 292 646

APPENDIX B

ASSOCIATION OF CANADIAN TEACHING HOSPITALS: MEMBERSHIP REQUIREMENTS

Requirements for Active Membership in the Association of Canadian Teaching Hospitals

The following is taken from page 6 of the Canadian Hospital Directory 1991-92:

Article II of the Constitution and Bylaws of the Association of Canadian Teaching Hospitals states that:

i) To be eligible for active membership, it is required of the hospital

a) That it be a party to a signed affiliation agreement or Act, or presents other acceptable evidence of affiliation with a University Faculty of Medicine, whereby the hospital provides for its active participation in the teaching of undergraduate students in medicine;

b) That, (subject to rare exceptions), it be approved for, and participate in the provision of specialty residency training programs in designated specialties which may include Family Medicine;

c) That, (subject to rare exceptions), it be approved for the provision of Preregistration Physician Training Programs;

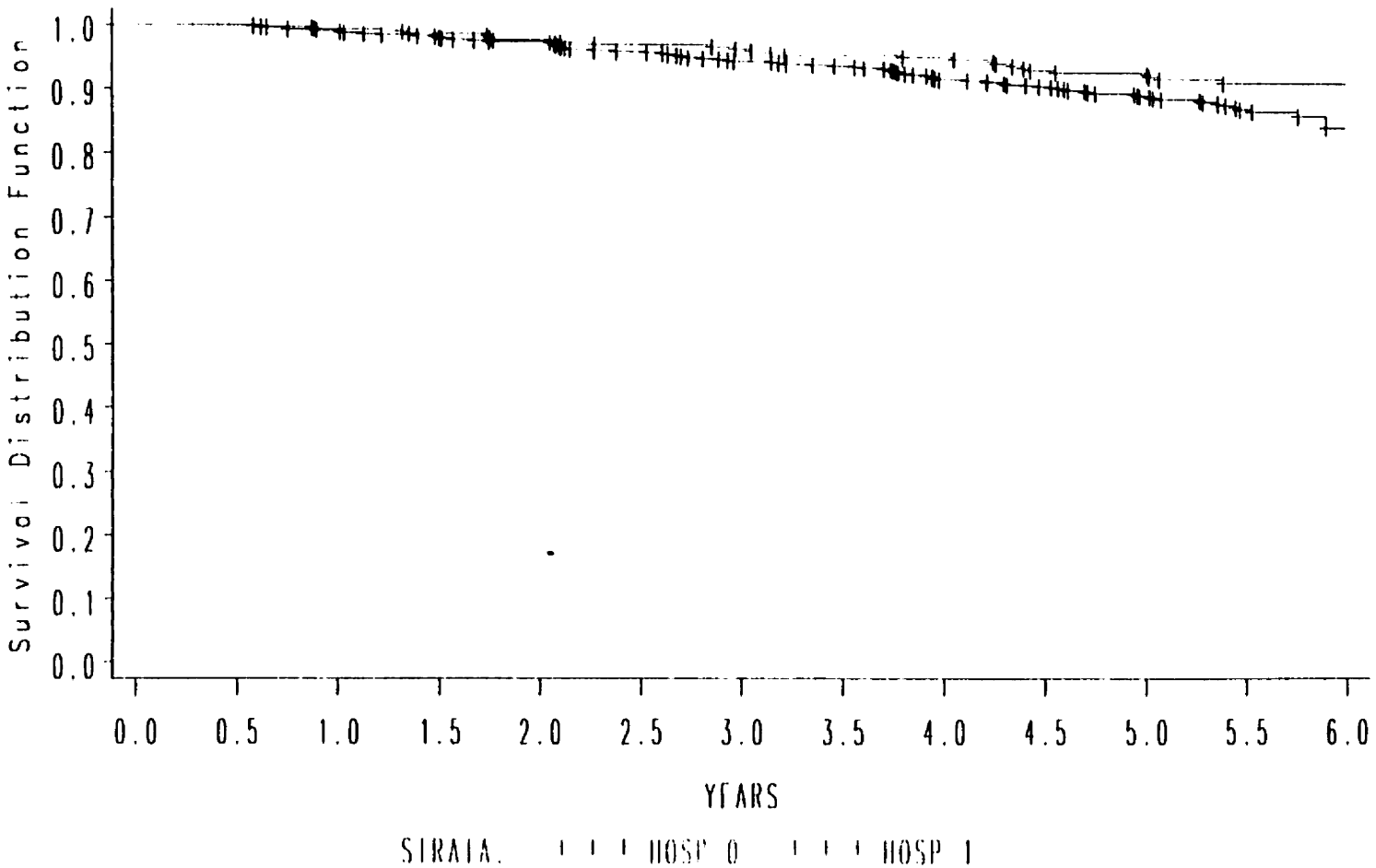
d) That, in the case of a specialty hospital, there be a demonstrated major participation in undergraduate and postgraduate medical education programs in the specialty field of the hospital.

APPENDIX C

KAPLAN-MEIER SURVIVAL CURVES

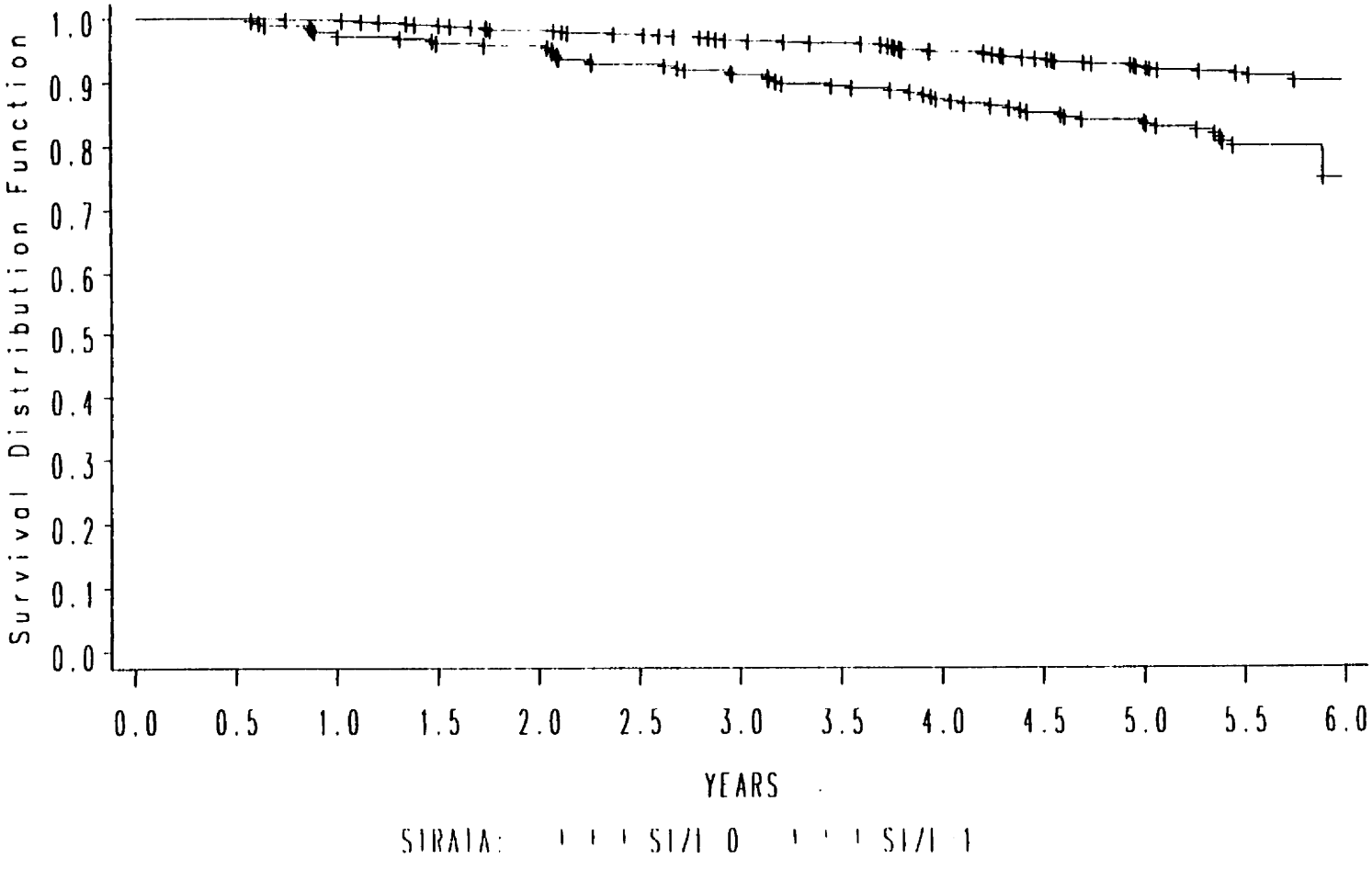
Survival by Treating Hospital

0-Community, 1 teaching



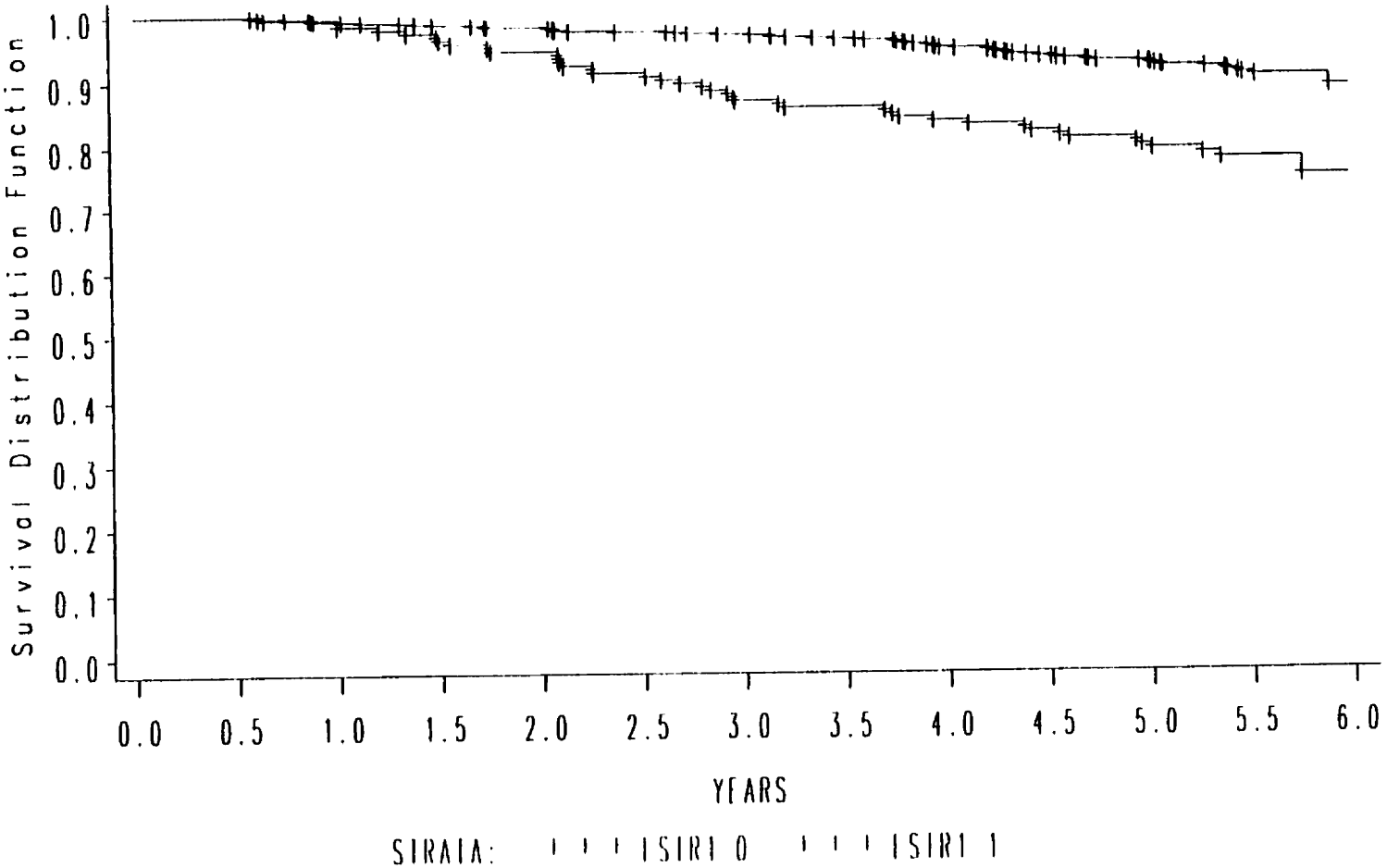
Survival by Tumor Size

0= <=20mm, 1= >20mm



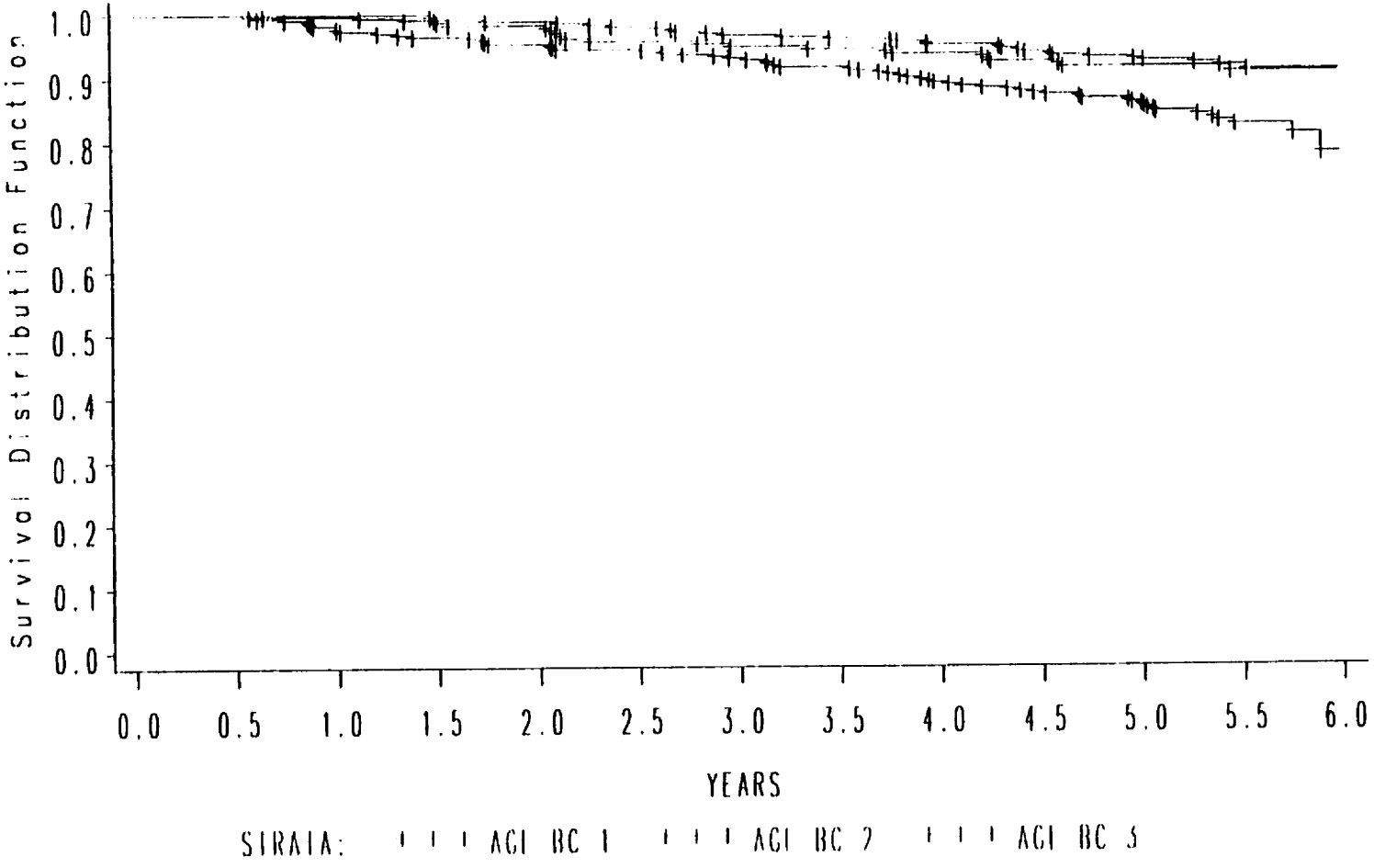
Survival by ER Status

0= positive/missing, 1= negative



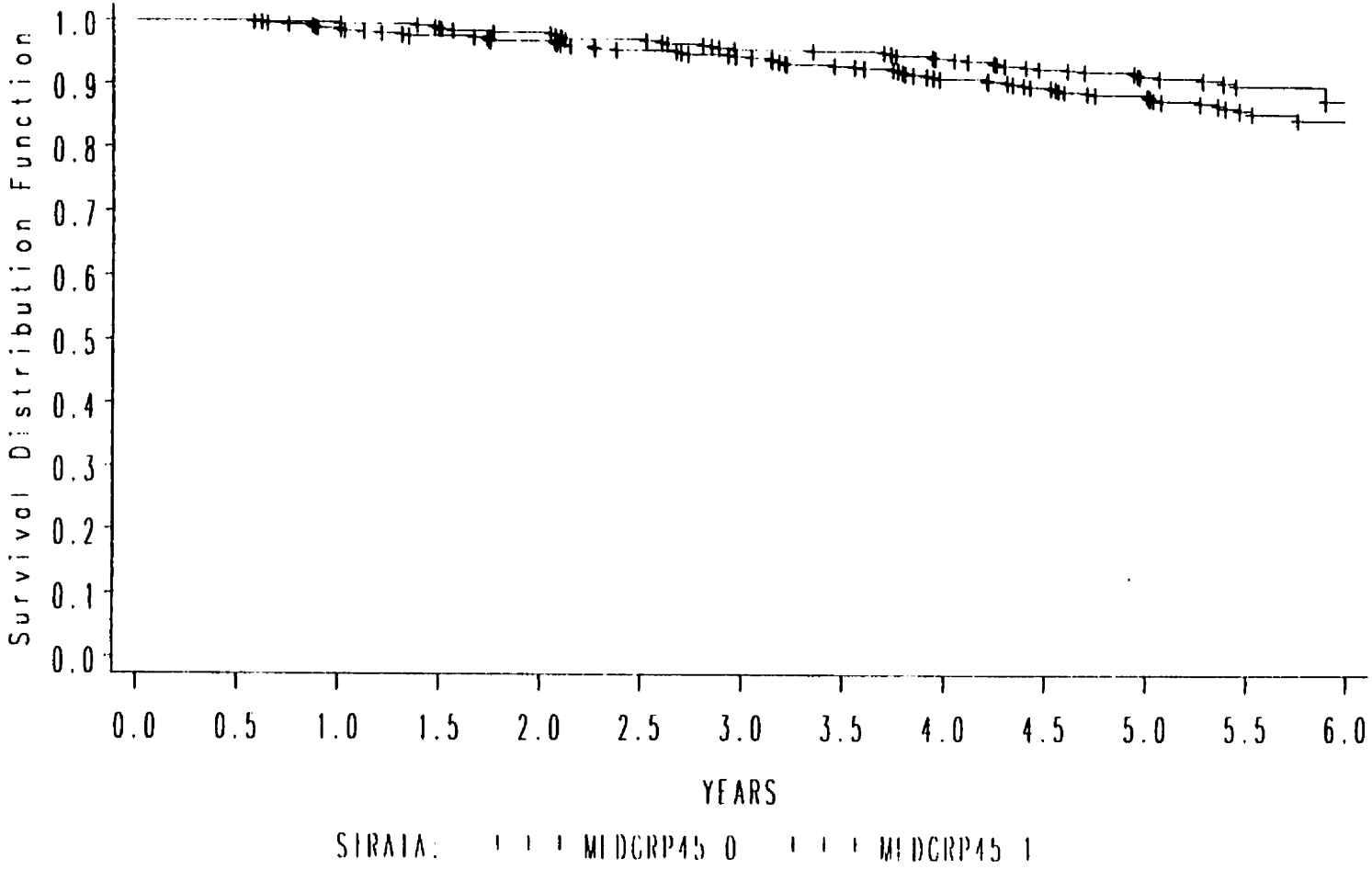
Survival by Age at Diagnosis

1= <50, 2 50-65, 3= 65-90



Survival by Median Income Group

0= <45,000, 1= > 45,000



APPENDIX D

POINT ESTIMATES AND CONFIDENCE INTERVALS FOR ADJUSTED SURVIVAL CURVES

Table D.1: Point Estimates and 95% Confidence Intervals
for Adjusted Survival Curves:
Women age 50-64 with ER-positive/missing tumours and who received radiation therapy

Survival Time	Tumours ≤ 20mm		Tumours > 20mm	
	Teaching Hospital	Community Hospital	Teaching Hospital	Community Hospital
1 year	0.995 (0.990, 0.999)	0.989 (0.981, 0.997)	0.978 (0.959, 0.998)	0.984 (0.970, 0.997)
2 years	0.986 (0.975, 0.998)	0.971 (0.954, 0.989)	0.941 (0.901, 0.984)	0.956 (0.928, 0.983)
3 years	0.973 (0.951, 0.995)	0.942 (0.911, 0.974)	0.885 (0.814, 0.962)	0.912 (0.865, 0.961)
4 years	0.959 (0.927, 0.991)	0.914 (0.871, 0.958)	0.830 (0.734, 0.939)	0.869 (0.805, 0.939)
5 years	0.944 (0.901, 0.987)	0.884 (0.829, 0.942)	0.775 (0.656, 0.916)	0.825 (0.744, 0.915)

Table D.2: Point Estimates and 95% Confidence Intervals
for Adjusted Survival Curves:
Women age 50-64 with ER-negative tumours and who received radiation therapy

Survival Time	Tumours ≤ 20mm		Tumours > 20mm	
	Teaching Hospital	Community Hospital	Teaching Hospital	Community Hospital
1 year	0.998 (0.997, 0.999)	0.996 (0.993, 0.999)	0.993 (0.987, 0.999)	0.995 (0.990, 0.999)
2 years	0.996 (0.992, 0.999)	0.991 (0.985, 0.996)	0.981 (0.968, 0.995)	0.986 (0.977, 0.995)
3 years	0.991 (0.984, 0.998)	0.981 (0.971, 0.991)	0.962 (0.937, 0.988)	0.971 (0.954, 0.988)
4 years	0.987 (0.977, 0.997)	0.972 (0.958, 0.986)	0.943 (0.906, 0.981)	0.957 (0.932, 0.981)
5 years	0.982 (0.968, 0.995)	0.962 (0.943, 0.981)	0.922 (0.875, 0.973)	0.941 (0.909, 0.974)