RISK OF RECURRENCE AND DEATH FOLLOWING BREAST CANCER: INFLUENCE OF PREGNANCY AND HORMONE REPLACEMENT THERAPY

by

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DOCTORAL DISSERTATION

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Abstract

Risk of Recurrence and Death following Breast Cancer: Influence of Pregnancy and Hormone Replacement Therapy

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Women diagnosed with breast cancer while still in their reproductive years face special concerns regarding future childbearing following initial cancer treatment. Previous epidemiologic studies have not identified an adverse effect of pregnancy after breast cancer on survival, but have been unable to rule out bias as an explanation for their findings. Use of hormone replacement therapy (HRT) might provide relief of menopausal symptoms for women who undergo early menopause following breast cancer treatment, were it not for concerns about an adverse impact on prognosis. Little scientific evidence exists to determine whether use of HRT after breast cancer affects prognosis. This study of women diagnosed with primary invasive breast cancer before age 45 from 1983 to 1992 examined the influence of subsequent pregnancy or HRT use on risk of recurrence and death from breast cancer. Information on pregnancies and HRT use were obtained from questionnaires or telephone interviews completed by subjects or proxy respondents for deceased subjects. Overall response to the survey was 73%.

Subsequent pregnancies were reported for 21% percent of women diagnosed before age 35, who had not undergone menopause or any surgical sterilization, compared with 1.4% of women diagnosed after age 35. There was no overall association between pregnancy following breast cancer and risk of recurrence or mortality. The adjusted relative risk for the association of subsequent pregnancy with recurrence was 1.0 (95% CI 0.3 – 2.9); the association with mortality was 0.9 (95% CI 0.2 – 4.2).

Nine percent of subjects reported use of HRT after breast cancer diagnosis. The adjusted relative risk of recurrence associated with any subsequent HRT use was 1.5 (95% CI 0.7 – 3.0), and the adjusted association of subsequent HRT use with mortality was 3.9 (95% CI 1.6 – 9.6). The results suggest that HRT use after breast cancer may be associated with an increased risk of mortality of threefold or more. However, further evidence that this finding cannot be explained by overreporting of HRT use by proxies is

being sought. Further studies of this question with accurate, prospective ascertainment of HRT use after breast cancer and recurrences are needed.

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DEDICATION

The author dedicates this work to her grandmother, Priscilla Terry Velentgas, who desired a career in medical science, but was not able to pursue this goal. Though she did not live to see her granddaughter graduate from college or from this Ph.D. program, these achievements would have pleased her greatly.

Introduction

The annual incidence of primary breast cancer among women aged 25-44 years has increased from 41 per 100,000 in 1974 to 50 per 100,000 in 1994 in western Washington state (Seattle SEER data), a somewhat greater increase than that observed in other areas of the United States (Miller 1992). The five-year survival rate among all women diagnosed with invasive breast cancer before age 45 in western Washington 1974-1995 is 76%; for women with local disease at diagnosis the five-year survival is 88% (Seattle SEER data). Concurrent with this observed increase in breast cancer incidence in young women has been a trend toward the postponement of childbearing to later ages than before (US Bureau of the Census 1984). As a result, there are more women living with breast cancer in recent years who have not yet completed or even begun their intended childbearing.

Women of childbearing age still make up only a small minority of newly diagnosed breast cancer cases, despite the increased incidence (Miller 1992). Yet these young breast cancer patients face special concerns regarding fertility and childbearing following treatment of their cancer. The few previous epidemiologic studies which have attempted to address the question of an effect of pregnancies after breast cancer on survival have not identified a negative effect of pregnancy, but have been unable to rule out bias as an explanation for their findings (Sankila 1994, Peters 1968, Cooper 1970, von Schoultz 1995). Difficulty in assembling a sufficiently large group of women with pregnancies following breast cancer to study these issues with sufficient power has also hindered such studies. Further research efforts are needed to provide breast cancer patients and their health care providers with sufficient information to make informed decisions regarding the possible risks of future childbearing.

Premenopausal women who receive chemotherapy or other treatments for breast cancer may undergo an early menopause as a result of such therapy (Hortobagyi 1986, Dickson 1991, Reichman 1994). Medically-induced menopause, generally abrupt in onset, may be accompanied by severe vasomotor symptoms and impaired sexual function (Bachmann 1994). These symptoms may be physically and emotionally devastating when they occur in women who were not prepared to face these problems at an early age, and who have already suffered the effects of having breast cancer on their body image and female identity (Schover 1994). In such situations, use of hormone replacement therapy (HRT) might provide substantial relief of symptoms (Meldrum 1987, Schonbaum 1991) and improved quality of life, were it not for concerns about an adverse impact on tumor recurrence and progression. Specifically, there is concern that use of an estrogen or combined estrogen/progestogen therapy may stimulate growth of any remaining malignant or premalignant cells (Spicer 1990, Theriault 1991, ACOG 1994, Marchant 1994). Little scientific evidence exists, however, to determine whether use of any form of HRT after breast cancer is predictive of poor prognosis.

The primary objectives of this study were to determine whether pregnancy or use of HRT after initial breast cancer diagnosis is related to risk of recurrent breast cancer and mortality in women diagnosed before age 45.

Chapter I: Background

A. Hormonal Mechanisms by which Subsequent Pregnancy or HRT Use May Affect Breast Cancer Prognosis

The most likely mechanism by which pregnancy or use of HRT could affect the risk of recurrence in women with a previous breast cancer is believed to be through promotion of growth of any remaining breast cancer cells (micrometastases) by estrogen and/or progestogen (Theriault 1994). Estrogen and progestogen have received a great deal of study in regard to their effects on breast tumorigenesis and growth. Much of this research has focused on their effects on cell proliferation (Dickson 1991), which is believed to be an essential step in the process of human breast carcinogenesis (King 1993).

In the normal mammary gland, estrogens promote ductal growth. Estrogens also appear to play a regulatory and synergistic role with other hormones, including progestogens, in the development of breast tissue (Topper 1980, King 1993). Progestogens promote development of alveoli and lobules from ducts in the normal mammary gland. Progestogens appear to have proliferative as well as differentiating effects (Clarke 1990); the proliferative activity of breast epithelium peaks during the luteal phase of the menstrual cycle when levels of progestins are highest (Staffa 1992). Some have proposed that the effect of progestogens is essentially anti-estrogenic, and thus anti-proliferative (Mauvais-Jarvis 1986). To date however, observation of an anti-estrogenic effect has been confined to normal endometrial tissue, whereas in normal breast tissue progestogens may also stimulate proliferative activity (King 1993).

The effects of estrogen on breast tumor cell proliferation appear to be dose-dependent (Sheth 1991). Estrogens stimulate proliferation of established breast cancer

at low or physiologic doses (Lippman 1976, Dickson 1988, Santen 1990), although pharmacologic doses can induce regressions of some breast cancers (Lippman 1976, Santen 1990). High pharmacologic doses of progestogens can also induce tumor regression of some breast cancers (Santen 1990), although the effect of lower physiologic doses is less clear.

A frequently stated concern regarding the possible effect of a subsequent pregnancy on breast cancer prognosis is that pregnancy could promote growth of dormant micrometasteses (Danforth 1991, Petrek 1994). It may, however, be possible that the levels of estrogen and/or progestogen during pregnancy, which are as much as several hundred times higher than normal (Cunningham 1993), would be sufficiently elevated to produce a beneficial effect on breast cancer prognosis. The underlying biologic mechanism for such an association, if it exists, is not clear, and the dose-dependent effects of these hormones are not well understood (Sheth 1991). Since the effects of estrogen and progestogen on proliferation of breast cancer cells depend additionally on the presence of other hormones and on tumor characteristics, it is difficult to extrapolate from the results of laboratory studies (which usually attempt to isolate the effects of a single hormone under precisely defined conditions) to draw conclusions about the likely hormonal effects of pregnancy on breast cancer recurrence. Furthermore, the various hormonal, immunologic, and physiologic changes that a full-term pregnancy exerts on the body constitute multiple "exposures" and could hypothetically exert a variety of effects on a woman previously diagnosed with breast cancer. Evidence from animal models has shown that while pregnancy and lactation occurring before administration of chemical carcinogens decreases tumor incidence (Dao 1960, Russo 1979), pregnancy occurring after carcinogen administration accelerates the growth of induced mammary tumors (Dao 1959, 1962, 1964).

An alternate hypothesis regarding the possible association of pregnancy subsequent to breast cancer and prognosis has been suggested. Human chorionic gonadotropin (hCG), a placental hormone, has been shown to reduce the incidence of mammary tumors in rats when administered prior to carcinogen exposure (Russo 1995a). A similar effect may be evident in humans, according to the results of one case-control study which examined the risk of breast cancer associated with past use of hCG in the treatment of infertility or to promote weight loss (Bernstein 1995). HCG has been shown to induce differentiation of the mammary gland in a manner similar to that of a full-term pregnancy (Russo 1995b), thereby leaving the breast less susceptible to initiation of carcinogenesis. Data from a rat model indicate that hCG may also affect the growth of mammary cells that have already undergone malignant transformation (Russo 1990). A decrease in the rate of cell proliferation of mammary cells in vitro has also been shown (Moviglia 1984, Russo 1985), suggesting the possibility that hCG exposure during pregnancy could reduce the risk of recurrence in women with previous breast cancer.

Although HRT is potentially a more easily defined and easily studied exposure than pregnancy, there is as yet insufficient understanding of the individual and combined effects of estrogen and progestogen on neoplastic mammary cells to predict the likely impact on breast cancer prognosis. The variety of possible HRT regimens in common use, and the likelihood of variation in effect according to tumor and patient characteristics present additional complexities. Most discussions of the issue of HRT use after breast cancer have been based on the underlying assumption that HRT is unlikely to have a beneficial effect on the course of the disease (Spicer 1990, Theriault 1991, ACOG 1994, Marchant 1994). A few authors have, however, postulated that certain combinations of estrogen and progestogen could prevent incident breast cancer

and possibly reduce the risk of recurrent breast cancer, based on some in-vitro studies and observations from animal models (Stoll 1989, Gambrell 1983).

The conflicting and speculative nature of these hypotheses regarding the effects of a pregnancy or HRT use on breast cancer prognosis illustrates how limited an understanding there is of the roles played by estrogens, progestogens, and other hormones in human breast cancer.

B. Studies of Pregnancy and Childbearing after Breast Cancer

It has been shown that the growth of human breast cancers can be influenced by exogenous and endogenous hormones, especially those tumors which contain estrogen and progestogen hormone receptors (Dickson 1991). On this basis, it is thought that the high levels of estrogens, progestogens and other hormones present during pregnancy might act to stimulate growth of some remaining breast cancer cells in women who have previously been treated for breast cancer (Danforth 1991).

No previous studies attempting to evaluate the effect of subsequent pregnancy on breast cancer survival have been able to convincingly dismiss this concern. Most reports have been from clinical case series where causal inference was hindered by extremely small sample sizes, and lack of any comparison series (Sutton 1990, Nugent 1985, Max 1983, King 1985, Rissanen 1969), or of an appropriate comparison series (Ariel 1989, Clark 1978). Furthermore, some of these studies report on small numbers of cases ascertained over a period of three to four decades (Ariel 1989, Clark 1978, Rissanen 1969), and are unclear regarding methods of following subjects to ascertain pregnancies, raising the likelihood of selection bias. None of these studies or case series have taken into account the fact that women who lived to become pregnant would necessarily have longer survival than a group of otherwise similar women in whom

there was no survival requirement (Sutton 1990, Nugent 1985, Max 1983, King 1985, Ariel 1989, Clark 1978, Rissanen 1969). All of these authors described the survival of women with pregnancies after breast cancer as being comparable to or better than what they had observed in similar patients without pregnancies. Among studies that actually conducted a survival analysis with a comparison group and adjusted for (at least) age, stage at diagnosis, and survival until the time of the delivery (Sankila 1994, Peters 1968, Cooper 1970, von Schoultz 1995), there has also been a consistent finding of better survival in the group which delivered children. One study of 23 women with pregnancies subsequent to breast cancer and a comparison group of 23 women with no pregnancies after breast cancer matched on age, stage, and time to pregnancy without recurrence found a lower risk of local and distant recurrent breast cancer among the pregnancy group (22%) than among the case-matched group (29%) (Dow 1994). One study that considered pregnancy outcomes other than live births reported that survival was no worse in women with these pregnancies than among women who did not become pregnant (Mignot 1986); another reported poorer survival (Clark 1978).

One explanation for these findings is a form of selection bias termed the "healthy mother effect" (Sankila 1994), by which the women who become pregnant are those with a better prognosis, and the comparison women may not be as healthy at the time of the pregnancy or delivery even if selected prognostic factors measured at diagnosis are equivalent. There is also very likely residual confounding by disease status at diagnosis which is not fully captured by adjustment for a few measured prognostic factors.

Though epidemiologic studies to date have consistently found that becoming pregnant or giving birth after breast cancer does not appear to be associated with worse survival, most have not been able to address this issue of "healthy mother" selection

bias. Dow et al., by matching comparison women to women with subsequent pregnancies on recurrences prior to the date of pregnancy (or index date), did account for this bias to some degree (Dow 1994). However, their study was small, relied on physician recall and medical record review for sampling, and ascertained women with subsequent pregnancies over a 40 year period (Dow 1994). Thus, breast cancer patients and their physicians still do not have reliable information regarding the potential impact of a pregnancy on breast cancer recurrence and survival to assist in making decisions about becoming pregnant.

C. Use of HRT after Breast Cancer and Prognosis

Evidence from a variety of sources suggests that certain hormonal exposures affect breast cancer prognosis. Significant differences in disease-free survival have been demonstrated between hormone receptor positive and negative breast cancer patients (Knight 1977, Tsangaris 1992, Aaltomaa 1991). Treatment with tamoxifen, an anti-estrogenic drug, has been shown to substantially reduce the risk of recurrence in premenopausal women with hormone receptor positive tumors, and to have a smaller effect in those with hormone receptor negative tumors (EBCTCG 1992). Oophorectomy has similarly been shown to reduce risk of recurrence and death in premenopausal women with breast cancer. (EBCTCG 1992) A number of studies have found that obesity or large body size is associated with decreased survival (Boyd 1981, Kyoguku 1990, Mohle-Boetani 1988). This association might be explained by higher levels of endogenous estrogen in obese women (Donegan 1978, Boyd 1981), but could also result from problems with tumor detection (Mohle-Boetani 1988), especially in premenopausal women who have less frequent mammograms based on current screening guidelines. Also, a few epidemiologic studies and an animal model

have suggested that timing of surgery in relation to the menstrual cycle can have an impact on risk of recurrence (Badwe 1991, Senie 1991, Ratajczak 1988).

The association of exogenous hormone use prior to breast cancer diagnosis and survival has also been described (Strickland 1992, Bergkvist 1989); survival among women with breast cancer who were users of estrogen-containing HRT at the time of diagnosis appeared to be somewhat better than that of past or never users. Though initial reports from various case series regarding an association between oral contraceptive use and survival of young women with breast cancer were reassuring (RCGP 1981, Rosner 1985), a more recent Swedish study found that women who started OC use at an early age had a lower survival rate when compared with women who never used OCs or started at a later age (Olsson 1988) . The authors reported that the estrogen and progestogen receptor concentrations of the primary tumor were significantly lower among OC users who began use at an early age (Olsson 1988). Another recent study (Holberg 1994) found a decreased hazard ratio for mortality for short-term users of OCs compared to never-users, and a non-significant increased hazard for longer-term use.

Little direct evidence exists regarding the effects of hormone replacement therapy following diagnosis on breast cancer prognosis. There are two reports in the literature of HRT given to small numbers of previously treated breast cancer patients (Stoll 1989, Wile 1993), and some debate in the form of medical opinion or literature review articles about the desirability of clinical trials of HRT in such patients (Wile 1989, Theriault 1991, Creasman 1991, Eden 1992, Lobo 1993, DiSaia 1993, Spicer 1993, Cobleigh 1994, ACOG 1994). Stoll reported that an unspecified number of postmenopausal women with previously treated breast cancer were treated with 3 or 6 months of combined estrogen/progestogen therapy if they suffered severe vasomotor

symptoms or genital atrophy (Stoll 1989). None of these patients were diagnosed with recurrent breast cancer over two years of follow-up. A 1993 report by Wile et al. describes the short term survival of 25 women who were given HRT after breast cancer, and did not present results stratified by stage, age, or hormone receptor status (Wile 1993). The authors conclude that "it is imperative that prospective trials be conducted to resolve the issue of the use of HRT in these patients" based on their report of 96% survival over a varied but brief (the average period of observation was three years) term of followup among this series of patients (Wile 1993).

To date, we know of no published report which provides clear evidence as to whether there are positive or negative effects of standard regimens of HRT on breast cancer prognosis. A generous interpretation of the reports from the two clinical series cited above would be that there may not be a large adverse effect of very short duration HRT given to some women that is observable over a few years of follow-up. There are no reports of longer-term use, despite the fact that the rationale used by some of those advocating clinical trials includes possible prevention of cardiovascular disease and osteoporosis (Vassilopoulou-Sellin 1994, DiSaia 1993, Bluming 1993, Wile 1993), which requires long-term use to provide long-term benefit. Clearly, many questions remain to be addressed before HRT could be considered standard care in any women with previous breast cancer.

D. Other Patient Characteristics and Breast Cancer Prognosis

In general, tumor characteristics such as tumor size and grade, lymph node status, and presence of estrogen and progestogen receptors and stage of disease have been shown to be the most important prognostic indicators for breast cancer (Carter 1989, Henson 1991, Neville 1992, Tsangaris 1992, Aaltomaa 1991). After these factors are taken into account, age, socioeconomic status, race and health insurance

coverage, and body size have been consistently found to be predictive of outcome (Boffetta 1993, Karjalainen 1990, Dayal 1982, Ayanian 1993, Donegan 1978, Boyd 1981, Newman 1986, Hebert 1988, Mohle-Boetani 1988, Kyoguku 1990, Vatten 1991, Holmberg 1994). The effects of family history and most reproductive variables known to be associated with breast cancer incidence are not clear (Ruder 1988, Lund 1991, Mohle-Boetani 1988); however, a few studies have shown that premenopausal parous patients have worse survival than premenopausal nulliparous patients (Black 1983, Korzeniowski 1994).

Chapter II: Methods

A. Overview of Study Design and Data Collection

A population-based cohort of 1249 women diagnosed with Stage I or Stage II invasive breast cancer before age 45 during the years 1983 through 1992 was followed for recurrences of cancer and deaths through May, 1996. All subjects had participated in one of two previous case-control interview studies of breast cancer in Western Washington conducted from 1986 through 1992. Previously interviewed subjects, or proxy respondents for deceased subjects, were mailed self-administered questionnaires with questions regarding initial course of treatment, recurrences of cancer, use of hormone replacement therapy (HRT), menstrual status, other medical information, and household information. Questionnaires sent to premenopausal subjects with no history of hysterectomy, oophorectomy, or surgical sterilization at the time of their original interview included additional questions regarding subsequent pregnancies, use of birth control, and fertility following breast cancer.

B. Cohort Identification

Eligible women diagnosed with a first primary breast cancer from January 1, 1983 through December 31, 1992 were initially identified from the Cancer Surveillance System (CSS). The CSS is a population-based cancer registry serving thirteen counties in western Washington state as part of the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute. Eligible cases were all primary invasive breast cancers diagnosed from January 1, 1983 through April 30, 1990 among white women born 1945 or later (n=898) and all primary invasive breast breast cancers diagnosed from May 1, 1990 through December 31, 1992 among white and non-white women 20 to 44 years of age (n=642). Eighty-four percent or 1,291 of

these 1,541 identified breast cancer cases participated in an extensive, in-person interview from 1986 to 1992 for one of two case-control studies of breast cancer at the Fred Hutchinson Cancer Research Center. These studies have been described more extensively elsewhere (White 1994, Brinton 1995). The most common reasons for non-interview were that the subject was deceased or too ill to be interviewed.

For the current study, all women interviewed in one of the previously described case-control studies with Stage I or Stage II disease constituted the study cohort (n=1249). Those who were not known to be deceased at the time of initial mailings (occurring between May 1994 and August 1995) and had not previously refused participation in future studies (n=24) were then contacted by mail and phone (n=1013).

C. Ascertainment of Deaths within the Cohort and Identification of Proxy Respondents

Deaths among the study cohort were ascertained primarily through the routine follow-up procedures of the Cancer Surveillance System of the Fred Hutchinson Cancer Research Center (CSS). Our study staff also identified a number of deaths of which the CSS had not yet been notified that were reported to us during routine telephone calls made to follow up on mailed study packets (n=36). Death certificates were obtained for 187 of the 208 deceased subjects who had died prior to May 1996.

Potential proxy respondents for the 208 deceased subjects were identified primarily from Washington state death certificates. For subjects who were married at the time of their deaths, we attempted to contact surviving spouses at the address given on the death certificate and enlist their participation. Of 187 subjects who died in Washington state for whom death certificates were obtained by May 1996, 144 were married. For non-married subjects (n=43), we contacted the informants whose names and addresses appeared on the death certificates and asked them who the most

appropriate person(s) would be to provide the information we sought about the deceased subject and for permission to contact this person(s). These non-husband or "other" proxies were most frequently mothers (27%) or sisters (24%), and less frequently other relatives (27%) or close female friends (7%) of the deceased. Additionally, we contacted one husband and one other proxy for 2 women who had died outside of Washington state (and for whom death certificates were not obtained), but whose deaths had been reported to us by these proxies at an earlier date.

Study packets were mailed to a total of 189 proxy study subjects (145 husband proxies and 44 "other" proxies) between September 1995 and May 1996.

D. Tracing and Follow-up of Subjects

Sources for obtaining updated addresses and/or telephone numbers for subjects who had moved since the time of their initial interview included: Washington State Department of Motor Vehicle Licensing tapes, the United States Postal Service's address correction service, regional telephone directories and national telephone directories on CD-ROM, Cole's city-wide directories, and information from physicians' offices. Eighty-seven percent of subjects not known to be deceased and 84 percent of proxies were located at a valid address and/or telephone number through these means (Table 1).

Reminder letters were sent and reminder phone calls were made to subjects and proxies who did not return their initial questionnaires to encourage their participation and answer any questions they might have had about the study. These follow-up procedures evolved over the two-year period during which subjects were contacted, as we relied on reminder letters only for the initial mailing in May 1994 and did not introduce phone call reminders until after the second mailing, in November 1994. In

addition to remailing of questionnaires upon request, subjects were offered the opportunity to complete the questionnaire over the telephone with an interviewer after phone follow-up began in November 1994.

E. Response to questionnaire

Completed questionnaires were obtained from 76% (n=790) of 1037 subjects alive when contacted and 59% (n=122) of 208 identified potential proxy respondents for deceased subjects. A detailed description of response status is provided in Table 1. Of 911 completed subject and proxy questionnaires, 84% were completed and returned by mail, and 16% were completed by telephone interview.

F. Questionnaire information

All information on the main exposures of interest and some covariate information were obtained by a self-administered or telephone-administered questionnaire for all subjects. Questionnaires sent to living subjects requested information on:

a. Treatments received by the subject following her initial breast cancer diagnosis, including types of surgery, radiation, chemotherapy, tamoxifen, or other treatments; and names of doctors and hospitals/facilities where treatments were received
b. Whether any recurrence of the subject's initial breast cancer or any new cancer had been diagnosed
c. Subject's menstrual status before and since initial breast cancer diagnosis, including whether periods stopped for a time following diagnosis and treatment

d. Subject's use of estrogen hormone replacement therapy (HRT) following breast cancer
e. Other medical procedures received since initial diagnosis, including oophorectomy, hysterectomy and surgical sterilization
f. Marital and household information

The series of questions about use of HRT were phrased so that only subjects who had used some form of estrogen as part of any HRT following breast cancer, with or without progestogen added to the regimen, would answer affirmatively that they had used HRT after breast cancer. Though a few respondents wrote in that they had used progestogen only, or other hormone therapy such as testosterone after breast cancer, these HRT regimens could not be uniformly captured by our instrument.

Questionnaires sent to the subcohort who were premenopausal and did not have a hysterectomy, oophorectomy, or report any surgical sterilization at the time of their original interview following diagnosis (n=830) contained additional questions regarding:

g. Pregnancies since initial diagnosis, including information on all pregnancy outcomes, dates, lengths of gestation and breastfeeding
h. Childbearing intentions before and after breast cancer
i. Use of birth control and fertility following breast cancer

Modified versions of these questionnaires were sent to proxy respondents. Questionnaires sent to proxies did not contain questions regarding the subject's childbearing intentions, use of birth control and fertility following breast cancer, but did contain questions regarding pregnancies after breast cancer.

Completed questionnaires were edited and coded manually in a three-step process by trained study staff. Subjects were telephoned to obtain missing information if questions had been skipped, and to clarify any discrepant information.

G. Other Sources of Information

In addition to self-reported (or proxy-reported) information on the main exposures, initial treatment, and other factors, data from the CSS was used to provide information on tumor stage and disease characteristics at time of initial diagnosis for all subjects. Also, items from the previous in-person interviews provided detailed information on reproductive history, family history of cancer, and other exposures prior to diagnosis.

H. Classification of Recurrence Information and Confirmation from Cancer Surveillance System Abstracts and Database Records

Information on recurrences of cancer were obtained by self-report and proxy-report from questionnaires, and supplemented with information from CSS abstract forms. Though information regarding recurrences of cancer in the ipsilateral breast or metastatic disease can frequently be found in CSS abstract forms as supplementary information, no systematic collection of such recurrence information by CSS was begun until July 1991. Following July 1991, recurrence information has not been uniformly collected, especially for cases whose initial primary breast cancer was diagnosed before 1991. New primary breast cancers in the contralateral breast, or of other non-breast sites have been recorded by CSS for the entire study period.

For subjects who reported being diagnosed with any recurrence of cancer, metastatic disease, or new primary cancer, CSS abstracts and database records were used to help classify new cancers as local or regional recurrences, distant recurrences,

new primary cancers, or contralateral breast cancers, and to confirm self-reported dates of these events. If no information regarding a self-reported recurrence of cancer appeared in the CSS abstract or database record for a given patient, subject self-report information alone was used, since the CSS ascertainment of recurrences is known to be incomplete. The earlier date for a given new cancer event was used regardless of source if the date given by the subject differed from that obtained from the CSS record.

If a subject reported no new cancer event occurring since her initial breast cancer diagnosis, other sources of information were not consulted; subject self-report was taken to be the "gold standard". Additionally, CSS abstracts were reviewed for a non-random sample of 165 subjects living at time of contact who completed questionnaires and provided recurrence information. Of 133 subjects who reported "no recurrences or new occurrences of cancer" following their initial breast cancer diagnosis, no (0) recurrences or other new cancer events were identified by CSS abstract review, whereas recurrences or other events were identified in CSS abstracts for 22 of 32 subjects who reported having a recurrence or other new cancer event in their questionnaires.

CSS records were consulted in a similar manner for all deceased subjects to help confirm proxy-reported dates of recurrences. Information regarding reported recurrences was found in the CSS records for 70 of 122 proxies. If information was not available in the CSS record to classify the type of recurrence as local/regional, distant, non-breast primary, or contralateral breast, it was assumed to be a distant recurrence of breast cancer.

Recurrences in the ipsilateral breast, or either breast in women whose initial cancer was bilateral, or in scar area or chest wall, or to regional lymph nodes (ipsilateral axillary lymph nodes or internal mammary lymph node) were counted as events in

analyses of recurrence-free survival. Recurrences diagnosed at any distant site except skin, including distant lymph nodes (contralateral axillary or internal mammary lymph nodes, and supraclavicular lymph nodes), were also counted as events in analyses of recurrence-free survival, unless they were specifically classified as new primary cancers by the CSS. The diagnosis date of the first relevant event was used in analysis when recurrences were diagnosed on multiple dates. Subsequent occurrences of cancer reported in the contralateral breast were not counted as events in analyses of recurrence-free survival, since these are usually considered new primary cancers unrelated to the initial primary (Fisher 1984). New primary cancers of sites other than the breast also were not counted as events in analyses of recurrence-free survival. Eight of 128 subsequent local occurrences of breast cancer were reported for which no information was available to identify the affected breast. These were assumed to have occurred in the ipsilateral breast, since 68% of all local recurrences with laterality information available from subject report and/or CSS data were reported to be ipsilateral.

I. Analysis

Fifty-eight women were pregnant at the time of or following breast cancer diagnosis. Ten of these women were pregnant at the time of their breast cancer diagnosis, but had no pregnancies conceived after diagnosis, and were not included in survival analyses comparing the risks of recurrence and death following breast cancer among women with and without subsequent pregnancies. One woman with unknown date of pregnancy onset (who had no full-term pregnancies after diagnosis), and one woman who was pregnant at the time of contact and had no other pregnancies following diagnosis were also excluded. Three additional women with recurrences occurring before onset of pregnancy were also excluded from these survival analyses. Three randomly selected subjects without pregnancies were then matched to each of 43

women who became pregnant following their initial breast cancer diagnosis and had no intervening recurrences of cancer. Matching criteria included age (within 7 years), and, for comparison women, a recurrence-free survival time greater than or equal to the interval between diagnosis and onset of pregnancy in the exposed subject. A total of 172 subjects (43 exposed women and 129 matched comparison women) were thus included in these analyses.

Sixteen women with recurrences of breast cancer before onset of HRT use, and 4 subjects whose reported reason for estrogen use was for treatment of their breast cancer were excluded from survival analyses comparing the risks of recurrence and death following breast cancer among women who did and did not use HRT after diagnosis. Four subjects with proxy-reported HRT-exposure information had missing dates of onset of HRT use; two of these subjects for whom no reason for HRT use was given were excluded from analysis to ensure that HRT was not used for breast cancer treatment, though the other two subjects with missing dates of onset of HRT use were not excluded, since the reason for HRT use was stated to be menopausal symptoms. Four randomly selected subjects who had not used HRT following diagnosis were then matched to each of 57 remaining subjects who had used HRT following their initial breast cancer diagnosis. Matching criteria included whether subjects had had a bilateral oophorectomy prior to diagnosis, and, for comparison women, a recurrence-free survival time greater than or equal to the interval between diagnosis and onset of HRT use in the exposed subject. A total of 285 subjects (57 exposed women and 228 matched comparison women) were included in survival analyses of HRT use after breast cancer.

Cox proportional hazards regression methods (Breslow and Day 1987) were used to compare the recurrence-free survival and overall survival following breast

cancer associated with pregnancies after breast cancer and use of HRT after breast cancer, and to control for confounding. Risk-set stratification was used to account for the matched set number, and other variables were controlled for by adding them to the regression model. Confounding variables were retained in the model if inclusion altered the hazard ratio by 10 percent or more.

Variables examined as potential confounders and/or effect modifiers included: age at diagnosis (<25 years, 25-29 years, 30-35 years, 36-39 years, 40 years or older), year of diagnosis, stage at diagnosis, lymph node status at diagnosis, tumor size at diagnosis (less than 2 cm vs. greater than or equal to 2 cm), treatments received for initial breast cancer, income at diagnosis (household income <$30,000 per year vs. ≥ $30,000 per year), parity prior to diagnosis (0 or 1 vs. 2 or more), and surgery type (mastectomy vs. other), ever use of HRT prior to diagnosis and menopausal status prior to diagnosis (for analyses of HRT use after breast cancer). Whether women had undergone an abrupt treatment-induced menopause, (either a bilateral oophorectomy occurring after diagnosis and before use of HRT or index date, or permanent cessation of menstrual periods following initial breast cancer treatment) was also evaluated as a confounder and effect modifier in analyses of HRT use after breast cancer.

J. Comparison of Respondents to Questionnaire with Non-respondents

Table 2 presents the demographic and disease characteristics at diagnosis (from CSS data), and Table 3 presents selected reproductive and other characteristics (from initial interview data) for participating and non-participating study subjects and proxies.

Among subjects living at time of contact, those who were older, diagnosed after 1988, of white race, and had more favorable disease characteristics were somewhat

more likely to participate in the follow-up study. Parity of 2 or more, and higher income were also associated with response.

Among potential proxy respondents for deceased subjects, higher income was most strongly associated with response. There was no clear pattern of response according to the subject's disease characteristics at diagnosis. Potential proxy respondents were somewhat more likely to respond if their wife or relative had been 35 years of age or older at diagnosis, and had not been diagnosed more recently than 1990.

Table 1: Response Status – Subjects Living at Time of Attempted Contact and Proxy Respondents

Eligible Subjects	Subjects Alive at Time of Contact		Proxy Respondents for Deceased Subjects	
	No. (N=1037)	%	No. (N=208)	%
Nonparticipants due to:				
Refusal*	54	5	16	8
Lost to follow-up	132	13	34	16
Non-response, no explicit refusal	61	6	17	8
No proxy respondent yet identified	—	—	19	9
Total Participants	790†	76	122	59

* Includes 24 subjects who were initially interviewed, but indicated they did not want to participate in future studies, and refusals due to illness.

† Includes one questionnaire received, was unlocatable at time of analysis.

Table 2: Demographic and Disease Characteristics of 1249 Previously Interviewed Subjects from Cancer Surveillance System data, by Response Status

	Alive at Time of Contact		Deceased at Time of Contact	
	Responded N=789 No. (%)	Did not respond N=253 No. (%)	Proxy responded N=122 No. (%)	Did not respond N=85 No. (%)
Age at Dx				
<25 yo	6 (0.8)	3 (1.2)	1 (0.8)	1 (1.2)
25-29 yo	38 (4.8)	24 (9.5)	7 (5.7)	9 (10.6)
30-34 yo	139 (17.6)	55 (21.7)	29 (23.8)	24 (28.2)
35-40 yo	330 (41.8)	100 (39.5)	62 (50.8)	31 (36.5)
40+ yo	276 (35.0)	71 (28.1)	23 (18.9)	20 (23.5)
Year of Dx				
1983-1986	127 (16.1)	63 (24.9)	50 (41.0)	34 (40.0)
1987-1988	156 (19.8)	60 (23.7)	28 (23.0)	22 (25.9)
1989-1990	222 (28.1)	60 (23.7)	26 (21.3)	13 (15.3)
1991-1992	284 (36.0)	70 (27.7)	18 (14.8)	16 (18.8)
Race				
White	750 (95.1)	232 (91.7)	121 (99.2)	83 (97.6)
Non-White	32 (4.1)	19 (7.5)	1 (0.8)	2 (2.4)
Unknown	7 (0.9)	2 (0.8)	0	0
Stage				
1	509 (64.5)	152 (60.1)	44 (36.1)	35 (41.2)
2	280 (35.5)	101 (39.9)	78 (63.9)	50 (58.8)
Lymph nodes				
0 positive	492 (62.4)	145 (57.3)	42 (34.4)	35 (41.2)
1 or more positive	268 (34.0)	92 (36.4)	74 (60.7)	47 (55.3)
Unknown	29 (3.7)	16 (6.3)	6 (4.9)	3 (3.5)
Tumor Size				
< 1 cm	83 (10.5)	19 (7.5)	5 (4.1)	0
1.0 cm - 1.9 cm	275 (34.9)	84 (33.2)	32 (26.2)	17 (20.0)
2.0 cm - 2.9 cm	211 (26.7)	63 (24.9)	23 (18.9)	25 (29.4)
3.0 cm - 3.9 cm	73 (9.3)	34 (13.4)	23 (18.9)	24 (28.2)
4.0 cm - 4.9 cm	32 (4.1)	14 (5.5)	6 (4.9)	4 (4.7)
5.0 cm or greater	50 (6.3)	18 (7.1)	15 (12.3)	8 (9.4)
Diffuse	7 (0.9)	1 (0.4)	7 (5.7)	1 (1.2)
Unknown	58 (7.4)	20 (7.9)	11 (9.0)	6 (7.1)
CSS grade				
Well differentiated	37 (4.7)	6 (2.4)	1 (0.8)	0
Moderately diff.	146 (18.5)	37 (14.6)	13 (10.7)	11 (12.9)
Poorly diff.	251 (31.8)	76 (30.0)	49 (40.2)	34 (40.0)
Undifferentiated	77 (9.8)	26 (10.3)	6 (4.9)	7 (8.2)
Unknown	278 (35.2)	108 (42.7)	53 (43.4)	33 (38.8)

Table 3: Selected Reproductive and Other Characteristics of 1249 Previously Interviewed Subjects from Interview data, by Response Status

	Alive at Time of Contact		Deceased at Time of Contact	
	Responded N=789 No. (%)	Did not respond N=253 No. (%)	Proxy responded N=122 No. (%)	Did not respond N=85 No. (%)
Parity before dx.				
0	202 (25.6)	79 (31.2)	28 (23.0)	15 (16.6)
1	136 (18.5)	52 (21.3)	25 (21.0)	13 (15.5)
2-4	436 (55.3)	118 (46.6)	68 (55.7)	55 (64.7)
5 or more	15 (1.9)	4 (1.6)	1 (0.8)	2 (2.4)
Pregnant at dx.				
No	782 (99.1)	248 (98.0)	118 (96.7)	85 (100)
Yes	7 (0.9)	5 (2.0)	4 (3.3)	0
Ever used HRT before dx.				
No	711 (90.1)	224 (88.5)	107 (87.7)	76 (89.4)
Yes	76 (9.6)	28 (11.1)	15 (12.3)	8 (9.4)
Don't know	2 (0.3)	1 (0.4)	0	1 (1.2)
Ever used OCs before dx.				
No	44 (5.6)	24 (9.5)	11 (9.0)	5 (5.9)
Yes	734 (93.0)	225 (88.9)	110 (90.2)	80 (94.1)
Don't know	11 (1.4)	4 (1.6)	1 (0.8)	0
Bilateral oopherectomy before dx.				
No	768 (97.5)	246 (97.2)	119 (97.5)	83 (97.6)
Yes	18 (2.3)	7 (2.8)	3 (2.5)	2 (2.4)
Don't know	2 (0.3)	0	0	0
Family history of br. cancer at dx.				
None	483 (61.2)	154 (61.4)	82 (67.2)	64 (75.3)
1st degree	124 (15.7)	49 (19.5)	11 (9.0)	7 (8.2)
2nd degree	175 (22.2)	47 (18.7)	27 (22.1)	13 (15.3)
Don't know	7 (0.9)	1 (0.4)	2 (1.6)	1 (1.2)
Yearly Household Income at dx.				
Less than $15,000	63 (8.0)	38 (15.0)	8 (6.6)	17 (20.0)
$15,000- $29,999*	151 (18.9)	78 (30.8)	35 (28.7)	24 (28.2)
$30,000- $49,000*	241 (30.5)	81 (32.0)	41 (33.6)	29 (34.1)
$45,000 or more *	329 (41.7)	54 (21.3)	37 (30.3)	15 (17.6)
Unknown	5 (0.6)	2 (0.8)	1 (0.7)	0

*Income categories differed somewhat between the two interview questionnaires, but are combined here.

Chapter III: Pregnancies after breast cancer and risk of recurrence and death

A. Results

Fifty-eight of 620 respondents who had not had a hysterectomy, oophorectomy, tubal ligation, or undergone natural menopause at the time of their initial breast cancer diagnosis reported a total of 89 pregnancies which coincided with or followed their diagnosis. Ten of these 58 women were pregnant at the time of diagnosis, but had no subsequent pregnancies. The proportion of women who became pregnant varied a great deal by the subject's age at diagnosis of breast cancer. Of the respondents who had not had a hysterectomy, oophorectomy, tubal ligation, or undergone natural menopause at the time of their initial breast cancer diagnosis (n=620), 21% of women diagnosed by age 35 reported any subsequent pregnancies compared with 1.4% of women diagnosed later than age 35. Table 4 shows the distribution of time from breast cancer diagnosis to pregnancy among the 43 women with subsequent pregnancies.

Table 5 compares women with pregnancies conceived after breast cancer and no intervening recurrences of cancer (n=43) to age-matched women with no subsequent pregnancies in regard to some demographic factors and disease characteristics, using information obtained from the CSS. Table 6 compares the medical treatments received by each group according to subject and proxy self-report, as well as reproductive factors reported by subjects at initial interview. Women with pregnancies after breast cancer had slightly more favorable disease characteristics at diagnosis than comparison women, and were less likely to have a mastectomy or to receive chemotherapy or tamoxifen or Megace therapy as adjuvant treatment. Women with pregnancies following breast cancer were more than twice as likely to have had no prior full-term

pregnancies at diagnosis. The frequency of various pregnancy outcomes is presented in Table 7.

Baseline survival curves comparing women with and without subsequent pregnancies are presented in Figures 1 and 2. The five-year recurrence free Kaplan-Meier survival among women with subsequent pregnancies was 0.93; the five-year recurrence free survival among women with no subsequent pregnancies was 0.87. The overall Kaplan-Meier survival at five years was 0.98 for women with subsequent pregnancies and 0.94 for those without subsequent pregnancies. Table 8 presents the adjusted relative risks (RRs) of recurrence of breast cancer and mortality for women with pregnancy after breast cancer compared with women with no subsequent pregnancies.

The crude RR for the association of pregnancy after breast cancer with recurrence of breast cancer was 0.8 (95% CI 0.3 – 1.9). With adjustment for the confounding factors of age and stage, the RR increased slightly to 1.0 (95% CI 0.3 – 2.9). The RRs for mortality from breast cancer were similar to those for recurrence (crude RR 0.8, 95% CI 0.2 – 3.0; adjusted RR 0.9, 95% CI 0.2 – 4.2). When analyses were confined to women with at least one full-term pregnancy after breast cancer, the adjusted relative risk of recurrence was 1.2 (95% CI 0.4 – 3.3), and the adjusted relative risk of mortality was 1.3 (95% CI 0.3 – 6.7). Adjustment for different combinations of tumor characteristics at diagnosis instead of or in addition to stage did not alter these associations. Adjustment for surgery type, chemotherapy, radiation, or tamoxifen or Megace treatment or combinations of these also did not materially alter these associations. Parity was also not shown to be a confounder of these associations.

To determine whether these relationships varied according to time between diagnosis and onset of pregnancy, we examined separately the relative risks of recurrence and death from breast cancer associated with pregnancy within 24 months of diagnosis, and with pregnancy onset more than 24 months after breast cancer diagnosis. For women with pregnancy onset within 24 months after diagnosis, the stage- and age-adjusted relative risk of recurrence was 1.3 (95% CI 0.4 – 4.1), and the adjusted relative risk of mortality was also 1.3 (95% CI 0.2 – 10.0). For women with pregnancy onset later than 24 months after diagnosis, the adjusted relative risk of recurrence was 0.3 (95% CI 0.1 – 2.6), and the adjusted relative risk of mortality was 1.0 (95% CI 0.1 – 11.5).

When we restricted both the pregnancy and comparison groups to women with Stage I disease, the age-adjusted risk of recurrence was 0.5 (95% CI 0.1 – 2.4), and the age-adjusted risk of mortality was also 0.5 (95% CI <0.1 – 5.5). It was not possible to estimate separately the relative risk of recurrence or mortality for women with Stage II disease at diagnosis using standard Cox regression methods, due to insufficient numbers.

Since fewer than half of women with subsequent pregnancies had information available from the CSS regarding estrogen or progestogen hormone receptor status, it was not possible to examine hormone receptor status as a confounder or effect modifier. We were also unable to examine the relative survival of women pregnant at diagnosis due to small numbers (n=10).

B. Discussion

This study found no overall association between pregnancy following breast cancer and risk of either recurrence or mortality from breast cancer. The observed

relative risks of recurrence and mortality associated with subsequent pregnancy did differ somewhat according to the length of time between diagnosis of breast cancer and pregnancy; however, confidence limits for these associations were wide.

Use of a self-administered, mailed questionnaire to assess exposures following breast cancer diagnosis means that our study results were vulnerable to possible response bias. If non-response, which was related to outcome status, also differed to an important degree by frequency of subsequent pregnancies, the observed RRs could be biased. This study does have the ability to assess comparability of some characteristics of respondents and non-respondents to a greater degree than is usually possible, due to the availability of CSS data and previously collected interview data on exposures prior to diagnosis for both respondents and non-respondents. Since non-response was somewhat more common for subjects diagnosed prior to 35 years of age, there could have been a slightly higher incidence of pregnancies among non-respondents as well, but whether this bias would be of sufficient magnitude to greatly alter observed risk estimates is unclear.

It also must be noted that the cohort of women defined as eligible for this follow-up study includes only women who were successfully interviewed in one of the two prior case-control studies. This exclusion of 15% of women diagnosed with Stage I or Stage II breast cancer before age 45 from 1983 through 1992 who were not interviewed limits to some degree our ability to generalize these results to the population of interest.

Reporting of the exposure of primary interest, live births after breast cancer, was not expected to be subject to a high degree of misclassification, even by proxy respondents (Fikree 1993). Though reporting of outcomes other than livebirths, especially by proxy respondents, may have been subject to some underreporting, our

findings did not differ when the exposed group was limited to only full-term pregnancies. This underreporting of other pregnancy outcomes, if greater among proxy respondents, would tend to underestimate any true association of subsequent pregnancy and adverse prognosis.

Our inability to evaluate whether the observed associations of subsequent pregnancy with recurrence and death varied according to estrogen and /or progestogen hormone receptor status was also a limitation of this study. A number of women in this study reported anecdotally that their physicians' recommendations regarding subsequent pregnancy were based on the hormone receptor status of their initial tumor, indicating that this is a question in the mind of at least some physicians and patients. The finding of an overall null association of subsequent pregnancy with adverse prognosis among women without regard to hormone receptor assay values is still reassuring, since a large adverse effect is less likely to exist for any subgroup.

An important strength of this study is its ability to account for the "healthy mother" confounding effect that most other studies of pregnancy after breast cancer and survival have not been able to address (Sankila 1994, Peters 1968, Cooper 1970, von Schoultz 1995). Subjects and proxy respondents were asked to report on the questionnaire whether they experienced any recurrences of cancer, and to give a date of the first such recurrence. Those subjects who answered positively to this question and all deceased subjects had their CSS records reviewed in order to more specifically confirm and classify new cancers. The collection of information on subsequent occurrences of cancer enabled us to make comparisons between women who had a pregnancy after their initial breast cancer diagnosis and a comparison group of women who had no new occurrences of cancer of any kind for at least the same length of time as between diagnosis and onset of pregnancy in the exposed group. Though the

ascertainment of recurrences in this study may have been incomplete, the comparison group was rendered more similar in terms of health status following diagnosis than in studies which only ensured that vital status of comparison women was equivalent at the time of onset of pregnancy (Sankila 1994, Peters 1968, Cooper 1970, von Schoultz 1995).

The use of a previously interviewed, population-based cohort of young women who have had breast cancer as the study population enhances the generalizability and validity of these study results when compared with reports based on clinical case series (Dow 1994, Peters 1968, Cooper 1970, Sutton 1990, Nugent 1985, Max 1983, King 1985, Ariel 1989, Clark 1978, Rissanen 1969).

Although previous studies of pregnancy subsequent to breast cancer diagnosis have consistently shown that women with pregnancies have better survival than women of similar stage or lymph node status at diagnosis who do not become pregnant (Sankila 1994, Peters 1968, Cooper 1970, von Schoultz 1995, Dow 1994), it has been unclear to what extent these results may be explained by the so-called healthy mother effect. The collection of information on any new cancer diagnoses following initial breast cancer enabled this study to reduce this effect by determining that the comparison group, women without pregnancies, had not had any recurrences of cancer for a period of time equivalent to the time from diagnosis to conception in women with pregnancies. When taken in context with the existing epidemiologic and clinical literature, this study provides additional reassurance that there is not an adverse effect of large magnitude associated with subsequent pregnancy. It also lends some support to the traditional clinical recommendation that women wait approximately two years after breast cancer diagnosis before becoming pregnant (Danforth 1991). This recommendation is usually based on the observation that the risk of recurrence following breast cancer is highest

for the first two years following diagnosis (Danforth 1991), rather than fear of an adverse impact of pregnancy. However, since we observed no increased risk of recurrence or mortality in women with pregnancy onset later than 24 months after diagnosis, this study further alleviates concern about an adverse effect of pregnancy on prognosis after such an interval.

Table 4: Interval between Breast Cancer Diagnosis and Pregnancy among 43 Women with Subsequent Pregnancies of any Outcome

Onset of pregnancy	No. (%)
Within 6 months of diagnosis	6 (14.0)
7-12 months after diagnosis	5 (11.6)
13-18 months after diagnosis	6 (14.0)
19-24 months after diagnosis	5 (11.6)
25-36 months after diagnosis	7 (16.3)
37+ months after diagnosis	14 (32.6)
Total	43

Table 5: Characteristics of Women with Pregnancies after Breast Cancer compared with Age-matched Women with No Pregnancies after Diagnosis

	Women with Subsequent Pregnancies N=43 No. (%)	Age-matched Women with No Pregnancies N=129 No. (%)
Marital Status at diagnosis		
Married	29 (67.4)	96 (74.4)
Other	14 (32.6)	33 (25.6)
Yearly Household Income		
Less than $15,000	4 (9.3)	15 (11.6)
$15,000- $29,999*	18 (41.9)	31 (24.0)
$30,000- $49,000*	6 (14.0)	39 (30.2)
$45,000 or more *	15 (34.9)	44 (34.1)
Unknown		
Stage		
1	30 (69.8)	73 (56.6)
2	13 (30.2)	56 (43.4)
Lymph nodes		
0 positive	30 (69.8)	69 (53.5)
1 or more positive	11 (25.6)	57 (44.2)
Unknown	2 (4.7)	3 (2.3)
Tumor Size		
< 2 cm	20 (46.5)	59 (45.7)
2.0 cm or greater	20 (46.5)	62 (48.1)
Unknown	3 (7.0)	8 (6.2)

* Income categories differed somewhat between the two interview questionnaires, but are combined here.

Table 6: Medical Treatment and Reproductive Characteristics of Women with Pregnancies after Breast Cancer compared with Age-matched Women with No Pregnancies

	Women with subsequent pregnancies N=43 No. (%)	Age-matched women with no pregnancies N=129 No. (%)
Surgery		
Mastectomy	16 (37.2)	74 (57.4)
Other Surgery	27 (62.8)	55 (42.6)
No Surgery	0	0
Received Chemotherapy		
No	21 (48.8)	32 (24.8)
Yes	22 (51.2)	97 (75.2)
Received Radiation		
No	14 (32.6)	61 (47.3)
Yes	29 (67.4)	68 (52.7)
Received Tamoxifen or Megace		
No	37 (86.0)	93 (72.1)
Yes	6 (14.0)	36 (27.9)
Ever Used Oral Contraceptives Before Diagnosis		
No	1 (2.3)	12 (9.3)
Yes	42 (97.7)	115 (89.1)
Missing	0	2 (1.6)
Parity Before Diagnosis		
0	23 (56.1)	27 (22.5)
1	8 (19.5)	26 (21.7)
2 or more	10 (23.3)	67 (51.9)
Missing	2 (4.7)	9 (7.0)

Table 7: Frequency of Different Pregnancy Outcomes among 43 Women with Pregnancies after Breast Cancer

Outcome	Women with or more pregnancies with this outcome after breast cancer No. (%)
Single live birth	30 (69.8)
Multiple birth	0
Stillbirth (> 20 weeks gestation)	0
Miscarriage (< 20 weeks gestation)	15 (34.9)
Induced abortion	10 (23.2)
Ectopic pregnancy	1 (2.3)
Pregnant at time of contact	3 (7.0)

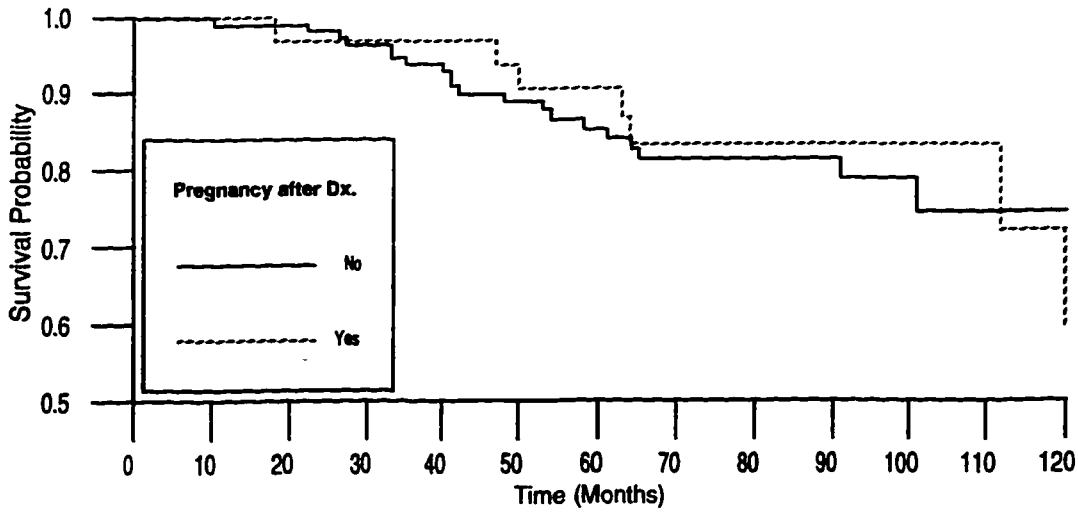

Figure 1
Recurrence-Free Survival following Breast Cancer among
Women with and without Subsequent Pregnancy

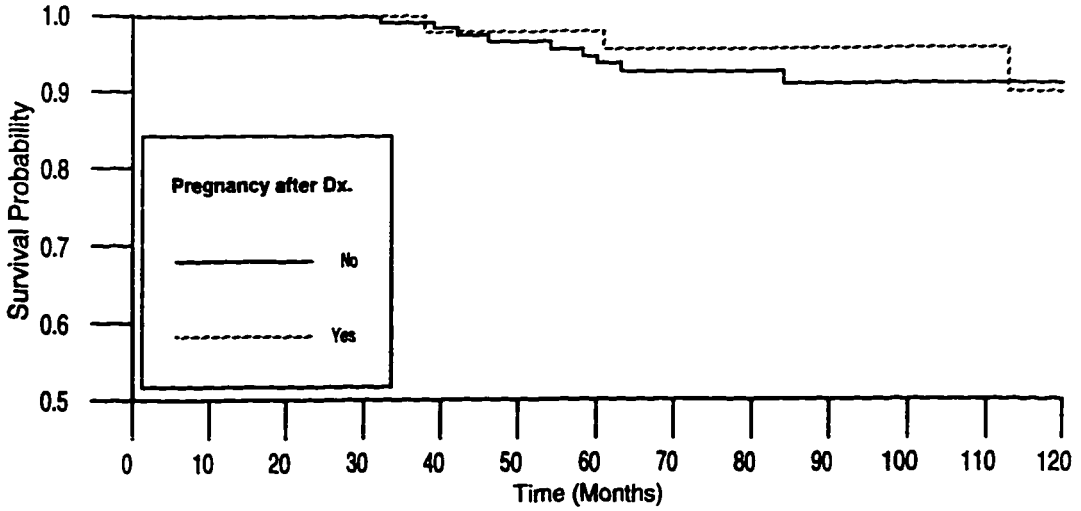

Figure 2
Overall Survival following Breast Cancer among
Women with and without Subsequent Pregnancy

Table 8: Relative Risks of Recurrence and Mortality from Breast Cancer associated with Subsequent Pregnancy among Women with Stage I or Stage II Disease at Diagnosis

	Recurrence		*Mortality*			
	Total Recurrences	Woman-months	Total Deaths	Woman-months	**Relative Risk of Recurrence*** *RR (95% CI)*	**Relative Risk of Mortality*** *RR (95% CI)*
Women with No Subsequent Pregnancies (N=129)	20	9,241	10	10,328	**1.0 (Referent)**	**1.0 (Referent)**
Women with Subsequent Pregnancies (N=43)	8	3,716	3	4,089	**1.0 (0.3 - 2.9)**	**0.9 (0.2 - 4.2)**

* Adjusted for age and stage.

Chapter IV: Use of HRT after breast cancer and risk of recurrence and death

A. Results

Seventy-nine of 911 respondents reported using some form of estrogen HRT for at least some time following their initial breast cancer diagnosis. 59 of these 79 subjects reported taking estrogen in pill form; less commonly reported was estrogen use in the form of vaginal cream (n=18), skin patch (n=6), or shots (n=2). Temporal patterns of use of HRT after breast cancer are shown in Table 9.

Tables 10 and 11 compare women who used HRT after breast cancer for purposes other than treatment of their breast cancer (who had Stage I or II disease and no intervening recurrences of cancer) to women who did not use HRT after breast cancer (matched on recurrence-free interval prior to the case's initiation of HRT use and on oophorectomy status prior to diagnosis) in regard to some demographic and reproductive factors, and medical treatments received. Women who used HRT after breast cancer had lower household incomes and were more likely to have Stage I disease than comparison women. They were also somewhat more likely to have used HRT before diagnosis, or to have had a bilateral oophorectomy or treatment-induced menopause after diagnosis (but before beginning HRT use).

Baseline survival curves comparing women who did and did not use HRT after breast cancer are presented in Figures 3 and 4. The five-year recurrence free Kaplan-Meier survival among women who used HRT after breast cancer was 0.80; the five-year recurrence free survival among women with no subsequent HRT use was 0.88. The overall Kaplan-Meier survival at five years was 0.88 for women who used HRT after breast cancer, and 0.97 for those without subsequent pregnancies. Table 12

presents the adjusted relative risks (RRs) of recurrence of breast cancer and mortality for women who used HRT after breast cancer compared with women who did not.

The crude RR for the association of HRT use after breast cancer with recurrence of breast cancer was 1.3 (95% CI 0.7 – 2.5). With adjustment for stage at diagnosis, the RR was 1.5 (95% CI 0.7 – 3.0). The crude RR for the association of HRT use after breast cancer with mortality from breast cancer was 3.3 (95% CI 1.4 – 7.8); the stage-adjusted RR was 3.9 (95% CI 1.6 – 9.6). These associations were not altered by adjusting for different combinations of tumor characteristics instead of or in addition to stage, for age, or for surgery type, chemotherapy or radiation treatment for initial cancer. Parity at diagnosis, menopausal status at diagnosis, or ever use of HRT prior to breast cancer also did not confound these associations.

We also explored whether adjusting for or stratifying according to whether subjects had undergone an abrupt treatment-induced menopause altered these risk estimates. The stage-adjusted relative risk of recurrence associated with HRT use after breast cancer was not altered by adjustment for treatment-induced menopause (RR 1.5, 95% CI 0.8 – 3.0); the RR of death associated with HRT use after breast cancer decreased to 3.7 (95% CI 1.5 – 9.4) with this adjustment.

Further adjustment for income in addition to stage and treatment-induced menopause slightly altered these risk estimates. The relative risks of recurrence and death adjusted for stage, treatment-induced menopause, and income were 1.4 (0.7 – 2.8), and 4.0 (95% CI 1.5 – 10.4) respectively. Since this adjustment did not meaningfully change these relationships and small numbers are a limiting factor, additional adjustment for income was not included for the other analyses presented.

When the HRT exposed group was limited to women who used HRT only in pill form or as a skin patch (and their matched comparison women, for analysis), the stage-adjusted relative risk of recurrence was 1.6 (95% CI 0.7 – 3.4), and the adjusted relative risk of mortality was 4.8 (95% CI 1.6 – 13.7). When women who had used HRT after breast cancer for less than six months were excluded (along with their matched comparison women), the adjusted relative risk of recurrence was 1.8 (95% CI 0.8 – 3.5), and the adjusted relative risk of mortality was 5.1 (95% CI 1.7 – 14.9).

When we stratified analyses of HRT use after breast cancer and survival according to stage of disease at diagnosis, we observed marked differences in these associations between subjects with Stage I and Stage II disease. Among subjects with Stage I disease at diagnosis, the RR of recurrence associated with HRT after breast cancer was 2.0 (95% CI 0.8 – 4.8), and the RR of mortality was 11.2 (95% CI 2.3 – 54.8). Among subjects with Stage II disease at diagnosis, the RR of recurrence associated with HRT after breast cancer was 0.5 (95% CI 0.1 – 2.6), and the RR of mortality was 0.6 (95% CI 0.1 – 3.3).

Among women who had not undergone a treatment-induced menopause (38 HRT-exposed and 168 comparison women), the stage-adjusted RR of recurrence was 1.6 (95% CI 0.7 – 3.4), and the stage-adjusted RR of death was 4.3 (95% CI 1.6 – 11.9). Further stratification by stage within this group again showed stronger associations of HRT use and survival among Stage I subjects, and the inverse among Stage II subjects. Among subjects with Stage I disease at diagnosis who had not undergone a treatment-induced menopause (28 HRT-exposed and 106 comparison women), the RR of recurrence associated with HRT after breast cancer was 3.0 (95% CI 1.1 – 8.2), and the RR of mortality was 11.7 (95% CI 2.3 – 57.8). Only 10 subjects who used HRT after breast cancer and 62 comparison subjects with Stage II

disease had not undergone a treatment-induced menopause; the RR of recurrence associated with HRT after breast cancer was 0.2 (95% CI <0.1 – 2.0), and the RR of mortality was 0.3 (95% CI <0.1 – 3.0) in this group. Cox regression models could not be fit for the subgroup who did experience treatment-induced menopause due to insufficient numbers.

Since less than half of women who used HRT had information available from the CSS regarding estrogen or progestogen hormone receptor status, it was not possible to examine hormone receptor status as a confounder or effect modifier of these associations.

B. Discussion

In this study, we observed a 50 percent increase in risk of recurrence of breast cancer associated with HRT use after initial diagnosis (95% CI -30% to 320%), and a stronger, three- to fourfold increase in risk of mortality which was statistically significant.

One possible non-causal explanation for this finding would be overreporting of HRT use after breast cancer by proxy respondents, but not by subjects themselves, thus artificially inflating the association of HRT use with mortality, but not (to the same degree) recurrence. This study design, which relied on proxy respondents for most subjects who had died but not for any living subjects, is not ideal for studying exposures which could be subject to differential recall between subjects and proxies. At least one study of the reliability of proxy reports of HRT use has concluded that proxy respondents are likely to underreport, rather than overreport use (Nelson 1994). However, those findings regarding HRT use prior to a diagnosis of sub-arachnoid hemorrhage (Nelson 1994) may not be generalizable to the proxy respondents in this

study, whose wives or relatives had undergone a wide array of medical treatments for breast cancer. If proxy respondents in this study were uncertain exactly which drugs the subject received, they could have confused use of a drug such as tamoxifen, for example, with estrogen use. If proxy respondents did report subsequent HRT use more frequently than it occurred and living subjects did not, this would produce an inflated estimate of relative risk of death associated with HRT use.. It is also likely that at least some proxies did not report subsequent HRT use for subjects who were so exposed, and to the degree that this underreporting was more common in proxy respondents than living subjects, there would be some reduction in the observed relative risk of death associated with HRT use. Validation of proxy reports of HRT use may help to provide a partial answer to these questions of bias. An effort to confirm proxy reports of HRT use after breast cancer with medical record and/or pharmacy data is now underway, since if overreporting of HRT use by proxy respondents can be ruled out, this would suggest that our results may underestimate the true association.

The use of a self-administered, mailed questionnaire to assess exposures following breast cancer diagnosis means that our study results were also vulnerable to possible response bias. Seventy-six percent of eligible subjects living at time of contact and 59% of proxy respondents for deceased subjects responded to the survey. If non-response, which was related to outcome status, also differed according to use of HRT after breast cancer, the observed RRs could be biased. This study was able to assess comparability of respondents and non-respondents to some degree, finding respondents and non-respondents similar in most respects except age at diagnosis and income. Hormone replacement therapy use did not vary by age, but was more common in women with lower incomes among respondents. Also, selective participation by users of HRT after breast cancer may have occurred, though it would seem more likely to occur among living women than among proxy respondents. Some influence of

response bias on these results in either direction cannot be ruled out. However, the more likely direction of the bias (based on possible over-representation of HRT users among living respondents, but not proxy respondents) would result in underestimation of any true association of HRT use with recurrence or mortality, and would not be a plausible non-causal explanation for the association we observed with mortality.

It must also be noted that the cohort of women defined as eligible for this follow-up study includes only women who were successfully interviewed in one of the two prior case-control studies. This exclusion of 15% of women diagnosed with Stage I or Stage II breast cancer before age 45 from 1983 through 1992 who were not interviewed limits to some degree our ability to generalize these results to the population of interest.

Since only subsequent HRT use for purposes other than breast cancer treatment was of interest in this study, we excluded any subjects for whom "breast cancer treatment" was given as a reason for use, and any subjects who had a recurrence before starting HRT use. If some recurrences prior to onset of HRT use were missed, particularly among deceased subjects with proxy-derived recurrence information, some subjects whose HRT use was for breast cancer treatment may have been included in the HRT-exposed group. If this misclassification was more common among deceased subjects, it may have served to falsely increase observed relative risks of recurrence and death associated with HRT use.

Exclusion of the 16 subjects with recurrences prior to HRT use from the HRT-exposed group without reincorporating them into the pool of non-HRT users from which the comparison group was drawn causes these risk estimates to be an imperfect, but close approximation of the associations with recurrence and mortality which would have been observed had these subjects had the same probability of inclusion as other

non-HRT users with the same values of the matching variables. The effect of this unnecessary exclusion would be to lower the risk of recurrence in the non-HRT exposed group, which would slightly inflate risk estimates.

The magnitude of the observed association of HRT use after breast cancer with mortality in this study (adjusted RR of 3.7), and more modest observed association with recurrence of breast cancer (adjusted RR of 1.5) is disconcerting. A true association with mortality of half that size would suggest that use of HRT after breast cancer could rarely be justifiable, given the large absolute risk of mortality from breast cancer that women already face. Though overreporting of HRT use by proxy respondents to the degree required to explain an association of this magnitude seems more extreme than would be expected, inability to account for differential recall by proxy respondents and living subjects is a major flaw of this study design. The lack of a stronger association of HRT use with recurrence may also be seen as lending support to this non-causal explanation.

Other considerations prevent us from discounting the possibility of an adverse affect of HRT use after breast cancer on disease outcome. First, the ascertainment of recurrences of breast cancer from subject and proxy self-report and CSS data was incomplete. Since women were not followed up according to a uniform protocol as is possible in a clinical trial, it is possible that misclassification of recurrence status (of a non-differential or systematic nature) could be sufficient to dilute a true stronger association of HRT use with recurrence. It is also true that the relationship of recurrence-free survival to overall survival is complex (Fisher 1991). In these data, stage, which is known to be an important predictor of survival following breast cancer (Ries 1994), was associated with a three-fold increase in risk of death (for Stage II vs. Stage I disease), but only a 1.7-fold increase in risk of recurrence. Thus it may be

concluded that the modest observed association of HRT use after breast cancer with recurrence does not in itself suggest that the stronger association with mortality is spurious. Second, further elevations in relative risk of recurrence and death were observed with duration of use of HRT of 6 months or more, strengthening to some degree the plausibility of a biological effect. Stronger associations with recurrence and mortality were also observed when the HRT-exposed group was limited to those women who had used HRT in pill or skin patch formulation. These formulations might be expected to deliver a more consistent dose of estrogen than would vaginal creams or shots, thus a stronger effect might be expected if a true relationship of HRT following diagnosis and survival exists.

To gauge whether the observed associations of HRT use after breast cancer with recurrence and death could reflect confounding by indication, we examined whether they varied according to whether women had experienced a treatment-induced menopause before onset of HRT use. If women with worse prognosis received more aggressive treatment and were thus more likely to experience abrupt onset of menopause with accompanying severe symptoms, then an artifactual association of HRT use with recurrence and death might be produced. Adjustment for this variable did not materially alter the observed associations, and when women with treatment-induced menopause were excluded, the relative risks of recurrence and death associated with HRT use after breast cancer increased slightly .

The worrisome nature of this study's findings regarding risk of recurrence and death associated with HRT use after breast cancer suggest a need for an observational study with accurate and systematic prospective ascertainment of HRT use and recurrence status among women with a previous breast cancer diagnosis. Evidence

from this study indicates that HRT use in this population has increased over time, which may make such follow-up studies more feasible now than in the past.

Table 9: Timing and Duration of HRT use after Breast Cancer among 57 Women with Subsequent HRT Use for Reasons other than Breast Cancer Treatment

	No. (%)
Onset of HRT use after breast cancer	
Already using at diagnosis (and continued to use)	3 (5.3)
6 months or less after diagnosis	5 (8.8)
More than 6 months but less than 1 year after dx.	5 (8.8)
A year or more after diagnosis	42 (73.7)
Unknown	2 (3.5)
Duration of HRT use after breast cancer	
6 months or less	21 (36.8)
More than 6 months but less than 1 year	6 (10.5)
A year or more after diagnosis	27 (47.4)
Unknown	3 (5.3)

Table 10: Characteristics of 57 Users of HRT after Breast Cancer compared with Women matched on Oopherectomy History Who Did Not Use HRT after Diagnosis

	Women who used HRT N=57 No. (%)	Women who did not use HRT N=228 No. (%)
Age at diagnosis		
<25 years	0	3 (1.3)
25-29 years	3 (5.3)	13 (5.7)
30-34 years	10 (17.5)	52 (22.8)
35-39 years	26 (45.6)	105 (46.1)
40 years or older	18 (31.6)	55 (24.1)
Year of diagnosis		
1983-1986	18 (31.6)	72 (31.6)
1987-1988	10 (17.5)	61 (26.7)
1989-1990	18 (31.6)	59 (25.9)
1991-1992	11 (19.3)	36 (15.8)
Yearly Household Income		
Less than $15,000	8 (14.0)	21 (9.2)
$15,000- $29,999*	18 (31.6)	53 (23.2)
$30,000- $49,000*	16 (28.1)	62 (27.2)
$45,000 or more *	15 (26.3)	89 (39.0)
Unknown	0	3 (1.3)
Stage		
1	43 (75.4)	129 (56.6)
2	14 (24.6)	99 (43.4)
Lymph nodes		
0 positive	43 (75.4)	127 (55.7)
1 or more positive	13 (22.8)	93 (40.8)
Unknown	0	3 (1.3)
Tumor Size		
< 2 cm	28 (49.1)	99 (43.4)
2.0 cm or greater	20 (35.1)	106 (46.5)
Unknown	9 (15.8)	23 (10.1)

* Income categories differed somewhat between the two interview questionnaires, but are combined here.

Table 11: Medical Treatment and Reproductive Characteristics of 57 Users of HRT after Breast Cancer compared with Women Matched on Oopherectomy History Who Did Not Use HRT after Diagnosis

	Women who used HRT N=57 No. (%)	Women who did not use HRT N=228 No. (%)
Surgery		
Mastectomy	28 (49.1)	129 (56.6)
Other surgery	29 (50.9)	99 (43.4)
No surgery	0	0
Received Chemotherapy		
No	21 (36.8)	76 (33.3)
Yes	36 (63.2)	152 (66.7)
Received Radiation		
No	24 (42.1)	101 (44.3)
Yes	32 (56.1)	127 (55.7)
Don't know	1 (1.8)	0
Received Tamoxifen or Megace		
No	38 (66.7)	135 (59.2)
Yes	17 (29.8)	79 (34.6)
Don't know	2 (3.5)	14 (6.1)
Had Bilateral Oopherectomy after diagnosis		
No	45 (78.9)	198 (86.8)
Yes	10 (17.5)	29 (12.7)
Don't know	2 (3.5)	1 (0.4)
Treatment-Induced Menopause*		
No	38 (66.7)	168 (73.7)
Yes	19 (33.3)	60 (26.3)
Postmenopausal at dx.		
No	54 (94.7)	208 (91.2)
Yes	3 (5.3)	20 (8.8)

* Includes women with bilateral oopherectomy after diagnosis and before index date, and women whose periods stopped completely following initial breast cancer treatment.

Table 11 (cont.): Medical Treatment and Reproductive Characteristics of 57 Users of HRT after Breast Cancer compared with Women Matched on Oopherectomy History Who Did Not Use HRT after Diagnosis

Used HRT Before Diagnosis		
No	46 (80.7)	203 (89.0)
Yes	11 (19.3)	24 (10.5)
Don't know	0	1 (0.4)
Ever Used Oral Contraceptives Before Diagnosis		
No	3 (5.3)	13 (5.7)
Yes	54 (94.7)	214 (93.9)
Missing	0	1 (0.4)

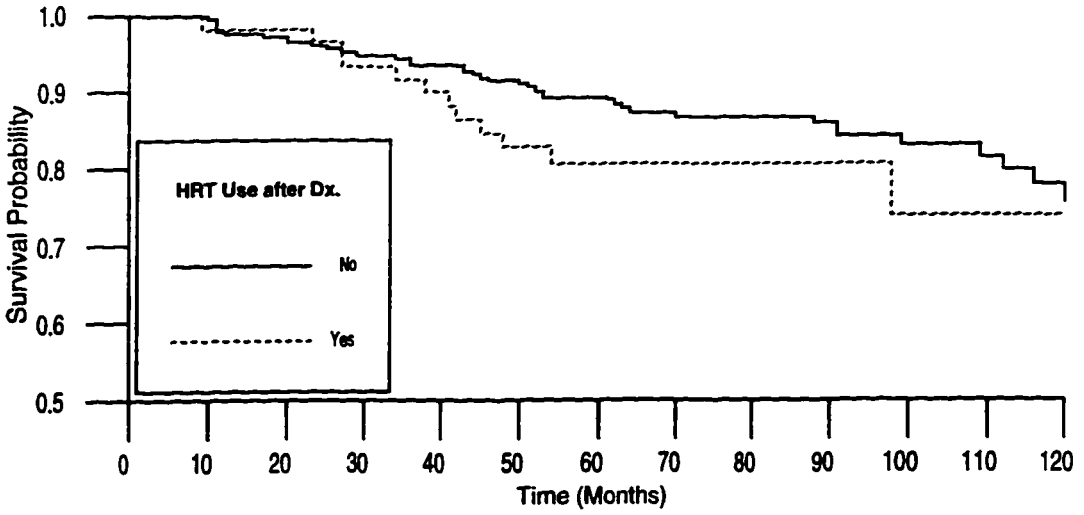

Figure 3
Recurrence-Free Survival following Breast Cancer among
Women with and without Subsequent HRT Use

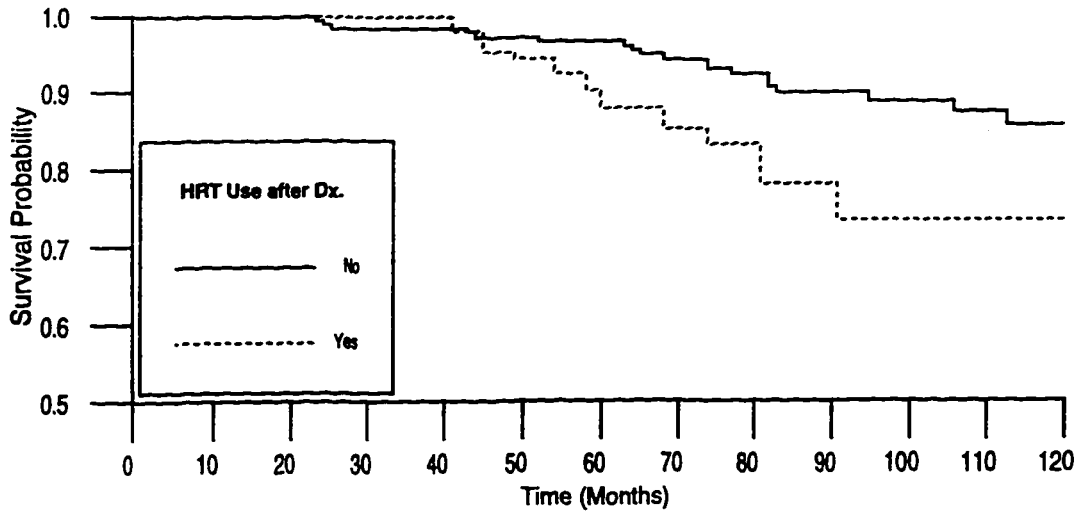

Figure 4
Overall Survival following Breast Cancer among
Women with and without Subsequent HRT Use

Table 12: Relative Risks of Recurrence and Mortality from Breast Cancer associated with HRT use after Diagnosis

	Recurrence		*Mortality*			
	Total Recurrences	Woman-months	Total Deaths	Woman-months	**Relative Risk of Recurrence*** *RR (95% CI)*	Relative Risk of Mortality* *RR (95% CI)*
Women who Did Not Use HRT after Diagnosis (N=228)	41	17,401	21	19,612	**1.0 (Referent)**	1.0 (Referent)
Women who Used HRT after Diagnosis (N=57)	12	3,960	10	4,493	**1.5 (0.8 - 3.0)**	3.7 (1.5 - 9.4)

* Adjusted for stage and treatment-induced menopause .

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