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PRINCIPAL INVESTIGATOR: Beth A. Mueller, Ph.D.

CONTRACTING ORGANIZATION: Fred Hutchinson Cancer Research Center
Seattle, Washington 98104-2092

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Beth A. Mueller, Ph.D.

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Seattle, Washington 98104-2092

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An increase in breast cancer incidence among younger women has been observed, thus many young breast cancer patients are faced with questions concerning their reproductive futures. At present it is unclear whether attempting childbearing may increase these women's risk of death. This project obtained data from a large sample of women to compare relative survival of women with and without births among young women with breast cancer. Data were obtained from three population-based registries (the Surveillance, Epidemiology, and End Results, or SEER Registries, in Seattle, Detroit, and Los Angeles). All women less than 45 years of age, diagnosed with breast cancer were identified in each of the three study regions. Their records were linked with birth certificates from each state to identify those (about 3%-4%) with a live birth after their initial diagnosis with breast cancer. Comparison subjects were identified from among young women with breast cancer in each region without subsequent births, matched on age and stage of disease at diagnosis, diagnosis year, race, and presence of multiple primary tumor. Date of last follow-up and vital status for all subjects are being updated from several sources, and relative survival will be compared among these two groups.

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Barbara Anne Mueller 9-23-97

PI - Signature Date

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I. INTRODUCTION

The nature of the problem and the study objectives have not changed over the previous year and are restated below. The review of previous work by other researchers has been abbreviated from the last report, however, and only includes results of studies published during the last year. A more comprehensive review of earlier literature is contained in the previous year's report.

I.A. Nature of the problem

The incidence of breast cancer among women less than 45 is increasing, and young women appear to have relatively poor survival. The prognosis may be even worse for women who are pregnant at diagnosis however, the effect on survival is unknown. As the increase in breast cancer incidence among younger women coincides with a trend towards delayed childbearing, information regarding the association of subsequent pregnancy and survival is needed so that women with breast cancer and their physicians can make informed choices concerning family planning.

At present there is no general consensus among physicians providing care to young women with breast cancer about how to advise them regarding their future reproduction , and the lay press clearly demonstrates that this is an issue of concern to those women affected. Current clinical recommendations concerning a waiting period of 2-3 years (the peak period of recurrence) after the conclusion of breast cancer treatment before attempting pregnancy are based on psychosocial and moral issues rather than scientific studies linking pregnancy with poorer survival. Women who survive their initial breast cancer treatment are justifiably confused concerning their future.

I.B. Recent related research by other investigators

Numerous factors have previously been noted to be associated with the risk of breast cancer, many of which involve conditions associated with endogenous hormonal alterations, most notably menarche, pregnancy, menopause, and the use of exogenous hormones. Since the last progress report for this project, there have been additional reports describing the associations of these conditions with breast cancer occurrence [Hulka, 1996; Newcomb et al, 1996; Daling et al, 1996; Ewertz, 1993; Leon et. al., 1995; Lambe et., al., 1995]. There has also been further work into the nature of increased susceptibility to breast cancer associated with family cancer history [Colditz, Rosner and Speizer, 1996; Malone et. al., 1996; Hulka, 1996]. The potential effect of these, and other characteristics, such as body mass index, alcohol, or smoking, on survival or recurrence, is still unclear. A recent study from the Netherlands reports no association of age at menarche, parity, family history, or use of oral contraceptives with breast cancer survival [Schouten, et. al., 1997]. Young age at first child birth was related to decreased survival (adjusted relative risk (RR): 1.69, 95% confidence interval (95% CI): 1.04-2.68) however, the authors state that this result may be due to chance alone, and that their study provided little support for the hypothesis that risk factors for breast cancer are related to

survival. Body mass index has, however, been associated with breast cancer survival in at least one study [Ewertz, 1993]. Data for many of these variables will be obtained from other databases for the study subjects in the Seattle region, allowing investigation of their potential impact on survival associated with subsequent childbirth. Having a multiple birth, or twinning, was associated with a slightly decreased risk (odds ratio (OR); 0.88, 95%CI: 0.78-0.99) of subsequent breast cancer in a Swedish study [Lambe et al., 1996], however no studies investigating the possible influence of this on survival were identified. Whether or not the index birth of our subjects who linked to the birth certificates was a singleton or higher order pregnancy is something that we may be able to ascertain from the study databases. This information is known to be available in the Seattle region, and its availability in other regions will be determined so that we may be able to evaluate the possible effect of this on survival related to subsequent childbirth.

Since the last literature search was conducted, a few more studies been identified that have evaluated recurrence or survival associated with pregnancy or childbearing after breast cancer diagnosis. In summary, childbearing subsequent to diagnosis has not reportedly been associated with an increased risk of death, except for situations where the pregnancy occurred soon after diagnosis. Recent clinical recommendations for women with breast cancer concerning future childbearing do not appear to have changed, with one recent report recommending a waiting period of two years after treatment before attempting pregnancy, and that women with advanced disease be discouraged from attempting pregnancies at all [DiFronzo and O'Connell, 1996]. In a follow-up study of women diagnosed at age <35 years in Greece, recurrence rate and survival among women with pregnancies were not found to differ from those without subsequent pregnancies, and offspring were reportedly healthy (median age of 51 months at end of follow up) [Malamos, et al., 1996]. In this population, 7% of subjects had a subsequent pregnancy 7-100 months after diagnosis, and cancer recurred in 14% of these, a level similar to that observed in non-pregnant women of the same age and stage of disease. Results from a study conducted in New Zealand evaluating survival in women pregnant or lactating after breast cancer diagnosis have also been reported [Lethaby, et. al., 1996]. Among women with breast cancer age less than 45 years, the incidence of pregnancy after diagnosis was 4%, similar to that observed in our data. Women pregnant at diagnosis had significantly more advanced disease than non-pregnant women, as did women lactating at diagnosis. When women lactating or pregnant at diagnosis were excluded, however, no significant differences in survival were found between those with and without subsequent pregnancies. Another study in women less than age 30 at diagnosis also found decreased survival among those with pregnancy-associated breast cancer, relative to those without pregnancies [Anderson, et., al., 1996]. In our data, we will evaluate separately women with births occurring 10 more months after diagnosis and those with pregnancies occurring sooner after diagnosis in order to measure survival within each group.

In addition to relevant studies related to risk factors for breast cancer occurrence and survival, there has been some further work reported concerning statistical techniques for evaluating time-dependent covariates in case-control studies [Hsieh and Lan, 1996] and follow-up studies [Malone, et. al., 1996]. Methods from the latter are being used in

developing analysis strategies for the present project, and we will consider the work reported in the former publication for its relevance to this project as well.

II. BODY OF PROGRESS REPORT

II.A. Study tasks completed

The study activities proposed in the revised statement of work that have been completed are listed below:

Task 1: Identification of exposed cohorts and protocol development. - Women <45 years of age at diagnosis of breast cancer during the years 1980-1993 were identified in the Seattle area, Detroit, and Los Angeles cancer registries. This includes 3,925 from Seattle; 4,496 from Detroit, and 6,962 from Los Angeles. Data tapes containing birth certificate information from 1980-1994 from Seattle and Michigan, and from California for 1980-1993 were obtained from each respective State Department of Health. A linkage program to link Registry data with birth certificate data was created in Seattle and made available to each of the other study regions, so that similar criteria were used in conducting linkages at each site. In all regions, data for women with breast cancer diagnosed during one calendar year were linked to birth certificates for the period of time including the same calendar year and all subsequent years of the study period. However, if a woman was known to be deceased, birth certificates for the years after her death were not searched.

Task 2: Identification and refinement of unexposed cohorts - A preliminary matching program was developed in Seattle for identification of the comparison women. The first version of the program included as matching criteria the following:

- age at diagnosis: (exact match)
- year of diagnosis: (1980-84; 1985-89; 1990+)
- stage of disease at diagnosis (exact match)
- race (exact match)

As matching was conducted within each region, exposed and comparison women were also matched on region. The potential pool of comparison candidates (essentially all women <45 years of age diagnosed during the same years but without a birth identified in the birth certificates) was first stratified into groups based on the matching criteria, and a variable designating the matching group identity was created. A matching group identity variable was also calculated for each exposed woman, based on these criteria, and then each exposed woman was allowed to draw as many comparison subjects as possible from the potential pool of candidates within the same matching group. The preliminary matching program was run in Seattle, and was made available to all sites. The data file resulting from this first version of the program were used in the preliminary results reported in the abstracts required by the DOD in May, 1997.

Results of the matching program were discussed in a teleconference described below. Relevant to our task of identifying unexposed comparison subjects, at this meeting we discussed the fact that a major issue of this study is matching a woman with a birth to a control with similar health status at the time of the birth to avoid a "healthy mother" bias. In the absence of questionnaire or medical records data about the subjects, only the data contained and updated in the registries, and via other methods of follow-up that do not include patient or physician contact can be used. We discussed the fact that cancer recurrence data specifically are not routinely collected by all registries, thus our best available indicator of health status at reference date is from data routinely collected, including vital status, date of last follow-up, and whether or not a second primary tumor has occurred. For these reasons, we decided that subjects should, in addition to other matching criteria, be matched on the presence/absence of a second primary tumor. Some conditions that might be identified in the registries, but which are not SEER reportable tumors (i.e., non-melanotic skin cancers and cervical carcinoma in-situ) were identified as those that should not be considered as multiple primaries within the matching criteria, however. This general concept was explored further with Dr. Lynda Voigt (Biostatistician, Seattle) and with Dr. Barbara McKnight (Biostatistician, University of Washington). Based on these discussions, the matching program was refined as follows:

- subject has another primary tumor (non breast) prior to diagnosis with breast cancer ==> match to comparison subject with another primary (non breast) tumor prior to diagnosis
- subject has another primary tumor within interval between diagnosis and reference date (birth date for exposed women, similar date for unexposed women) ==> exclude from analysis
- subject has another primary tumor subsequent to reference date ==> do not use as matching criteria, but describe in both groups and evaluate for effect on outcome.

An additional concern about the first matching program was that the pool of potential comparison subjects appeared not to be matched with equal probability to exposed subjects within the same matching identity group. (The program allowed an exposed woman in one matching identity group to be matched to up to up to 12 eligible comparison subjects within the same matching identity group. This resulted in there being fewer candidates in that stratum for the next exposed woman to be matched to.) Because of this, some exposed woman had many matched comparison subjects, whereas others had few or none. The program was revised to correct for this by including an algorithm that gave all unexposed subjects within a stratum equal probability of being selected as a match for an exposed subject within the same stratum.

The second version of the matching program was developed in Seattle and made available to all regions in July, 1997. Each region modified the program for their own data and produced new data sets in August, 1997. Data resulting from the second version of this matching program have been used to produce this report.

Task 3: Follow-up subjects to ascertain survival status - Status of each region with respect to follow-up protocols was also discussed in a teleconference (described below). At least annual updates of the registry data files are conducted at each registry site including linkage with vital records data to ascertain survival status. More active follow-up is conducted to some extent routinely in all regions via regular contact with hospital tumor registries contributing to each SEER registry. Follow-up of study subjects identified as exposed (having births subsequent to their diagnoses) has been conducted via these mechanisms. Follow-up of study subjects identified as unexposed through 1996 (or the date of the last routine vital records linkage at each site) is being conducted via these mechanisms, however, further follow-up of unexposed subjects is not possible until the matching program is finalized within the next two months. In all regions, further follow-up is available by checking registry resources including, in addition to vital records, updates of the Master Registry file to ascertain more recent status at last follow-up, searches of Department of Licensing data files (driver's licenses), and possibly phone records and/or InterNet search programs (similar to national phone books) such as "Switchboard". In Seattle, active follow-up will also include ascertainment of subject status in other research studies they may have participated in after their diagnoses. In Los Angeles, the Tracing Lab has conducted active follow-up on all potential subjects in their region via a credit bureau search. The Los Angeles registry Master File has been updated and the update of the analysis subfile will follow.

Description of Teleconference - A telephone conference call session was held on Thursday, March 6, 1997, at 10:00am (Pacific time). Attending the conference were Dr. Beth Mueller (PI, Seattle) and Ms. Janet Kelly (Research Coordinator, Seattle); Dr. Dennis Deapen (PI, Los Angeles); and Mr. Asim Kahn (Study Coordinator, Detroit). Dr. Simon (PI, Detroit) was unable to attend due to illness, however he reviewed the minutes of the meeting with Mr. Kahn and Dr. Mueller subsequently. At this meeting, issues related to the matching program and follow-up procedures were discussed as described above. In addition, we discussed our progress to date, study deadlines, and the following:

- ***Possible restriction of subjects by histology*** (raised as an issue for analysis by Dr. Simon in email message prior to the teleconference). We agreed that because survival (as well as treatment and whether or not a woman may attempt pregnancy) may be differ markedly in women with tumors of specific histological types (e.g., lymphomas or sarcomas) we will probably make restrictions in some sub-analyses to exclude certain groups of women. However, all histologic types would be included in building the general analysis files so that analysis of the study question in these subgroups can be conducted as numbers permit.

- ***Demonstration of the accuracy of the linkage protocols*** - The summary of the last annual report of study progress indicated that validity of the linkage protocol needed to be documented. It has been possible to do this using Seattle data. In Seattle, a portion of subjects had an interview in which they were queried about their pregnancies after diagnosis. Based on this sample (about 400 subjects) we determined that, of subjects who linked with birth certificates, 86% reported they'd had a live birth; 3% reported a

pregnancy without a live birth (miscarriage); and 11% reported having no pregnancies (although many of these reported they had adopted, which would explain why we were able to link birth certificates). Of those reporting miscarriages or no births, it is possible that births occurred subsequent to their interview. Furthermore, in Washington, the records of infants adopted at birth contain the names of the adopting parents. Interpretation of the results will take into account that a proportion of the births identified by certificate linkages may not represent real pregnancies, but are the result of adoptions. There was some discussion at the teleconference about the possibility of ascertaining whether or not specific birth record linkages represented adoptions; however, because of confidentiality requirements of the Department of Health in each state, this information is not available. It may be helpful for us to try to determine if the rates of adoption differ among the states, in order to understand if similar levels of over-reporting of birth events to subjects (because birth certificates may list the names of adopting mothers) are likely to occur in all regions. Because a portion of women in our exposed group may not truly have had births, this would make the exposed group more like the comparison group, and would have the effect of biasing our results towards the null.

Of cases who did not link to birth certificates, 95% reported they had no pregnancies; 4% reported pregnancies without births (and thus wouldn't have been picked up in birth certificates); and <1% reported live births (although they reported that the births occurred out of state). This indicates that the accuracy (sensitivity) of the birth information for the comparison group linkage is very good (approximately 95%); for all instances the linkage program gave the most appropriate answer, given the data sources. We need to be aware that there is a small proportion of women (<1%) in our comparison group who actually may have had births that were not identified by the records linkage because they occurred out of state. This kind of misclassification would result in making the comparison group more similar to the exposed women, biasing results towards the null. In interpreting results of this study, it may be helpful for us to obtain rates of migration for young women in each state from the U.S. Census. If the rates for all three regions are somewhat similar, then the proportion of women with out of state births (unreported) in the comparison groups in all regions is likely to be similar.

- ***More active inclusion of biostatistical consultants into the study*** was also discussed, as the data analysis and interpretation phases commence and the logistical and programming tasks become less time consuming. Drs. Deapen and Simon are familiar with Dr. Lynda Voigt because they have worked with her previously. Since the teleconference, Dr. Voigt (and her associate, Ms. Kara Cushing, a Masters degree level biostatistician) and Dr. Mueller have met frequently, including a meeting with Dr. Barbara McKnight, a senior biostatistician with expertise in survival studies who frequently consults with investigators at the Fred Hutchinson Cancer Research Center. Results of these consultations related to the matching program were described above.

- ***Replacement of Seattle Study Coordinator*** - At the teleconference, we discussed the fact that Ms. Kelly, the Seattle Study Coordinator, was leaving the project because of her imminent marriage and relocation to a different state. She was

commended for her superior work in helping set up the study and managing many difficult data related and organizational tasks. Plans for bringing her replacement, Ms. Aruna Kamineni, on board two weeks prior to Ms. Kelly's last work day were presented and approved by all investigators. Ms. Kamineni has been working with the project as Seattle Study Coordinator since July, 1997.

II.B. Study tasks in progress

Related to Task 2: Refinement of unexposed cohorts - is underway presently. An evaluation of the matched comparison subjects is being conducted concurrently with preliminary analyses resulting in the tables contained in this report. A meeting or conference call with the investigators, study coordinators, and biostatistical consultants, will be conducted within the next 2 months to discuss our findings and make recommendations for any necessary modifications to the matching program. It is anticipated that any modifications would be minor. However, because of the importance of making sure that any "healthy mother" effect, a potentially serious source of bias, is removed to the greatest extent possible, considerable efforts are being made to ensure that the matching step is conducted appropriately. Our revised statement of work tentatively indicated that this step would be completed by Month 12 of the 3rd year (October 1997). For the reasons mentioned above, it is anticipated that an additional 2-3 months will be required for this activity.

Related to Task 3: Follow-up of subjects - will continue at all regions. Los Angeles has conducted a credit bureau search for all potential subjects and will refine these data so that updated date of last follow-up and vital status variables can be incorporated into the analysis database for subjects. Detroit and Seattle have conducted follow-up using the routine mechanisms available at these SEER sites, and will update their analysis files from each registry's Master file as soon as they are finalized. Seattle has begun to conduct additional follow-up using information from recently conducted, separate research studies to ascertain vital status. It is anticipated that this activity will be concluded within the next 4 months.

Task 4: Obtain data for subset analysis from Seattle - Research activities at the Fred Hutchinson Cancer Research Center that may have involved young women with invasive breast cancer have been identified by Ms. Kelly, who initiated contact with the respective study coordinators for access to data, and obtained blank copies of the questionnaires used in each of these studies to identify relevant variables. Ms. Kelly's replacement, Ms. Kamineni, will review the prior work in this area so that after the analysis file containing exposed and comparison subjects is finalized for the Seattle area, she can work with the study coordinators to create a subfile of Seattle area data only, containing additional variables including information related to other factors potentially related to breast cancer occurrence (e.g., use of oral contraceptives, body mass index, reproductive history, family history, etc.).

II.C. Study tasks remaining and relevant plan for each task

Task 5: Data editing, analysis and manuscript preparation - Many aspects of data editing have been in progress since the study began. This includes creation of a uniform data dictionary for registry and birth certificate data from all site, a coding guide, and examination of preliminary data obtained at each phase of the study. Data from all 3 sites have been merged previously (initially, and again after the matching program was revised), and procedures for transferring data electronically and for editing and merging files have been developed. We anticipate that analysis of the final combined dataset will begin in early 1998, and that subset analysis of Seattle data will begin shortly afterwards. In preparation for data interpretation and writing of results, an updated literature search was performed, the results of which are described in the Introduction section. Preparation of manuscripts is likely to begin during the last 2 months of the study, with refinement and editing of manuscripts, preparation of manuscripts for submission to scientific journals occurring subsequently.

III. RESULTS TO DATE (CONCLUSIONS)

III.A. Result of data linkages

The number of women, <45 years of age, with invasive breast cancer identified in each region during the study period included 3,925 in the Seattle area, 4,496 in Detroit, and 6,962 in Los Angeles (Table 1). Because data for 1994 were also available at the time the linkage was conducted in Seattle, this year was also included in the linkage for that site at no additional cost. Birth certificate records for 1980-1993 were obtained in each state. In Seattle and Detroit, because of the nature of the existing agreements between the Cancer Registries and the Department of Health, access to an additional year of birth certificate data was also possible, and data from 1994 birth certificates were used in conducting the linkages at no extra cost. This was done to increase the number of exposed subjects (those with births after diagnosis) with a resultant increase in statistical power. In Los Angeles, the linkages were conducted beginning with the most recent years of data. When data for 1980-1981 were examined, it was learned that the birth certificates for California do not contain the mothers' names or any other identifier that could be used to link data (like Social Security Number). For this reason, it was not possible to link registry data to these two early years of follow up. As relatively few linkages were identified in these early years of follow-up at the other two sites, it is likely that few births were missed because of this. As the proposed method of analysis (Cox Proportional Hazards Regression) relies on person-time of follow-up with left censoring occurring at the subject's date of childbirth, use of slightly different years of diagnosis and follow-up for the subjects at different sites will have no impact on the analysis technique.

Table 1: Number of women (< 45 years) with a first, invasive breast cancer, and proportion with subsequent births identified by birth certificates by region

	Seattle	Detroit	Los Angeles	All Regions
Years of diagnosis	1980-1994	1980-1993	1980-1993	1980-1994
No. women with invasive breast cancer	3925	4496	6962	15,383
Years of birth records searched	1980-1994	1981-1994	1982-1993	1980-1994
No. women with births identified through birth certificates				
Total births identified (%) [a]	141 *(4%)*	225 *(5%)*	278 *(4%)*	643 *(4%)*
Birth <10 months after dx	*22*	*30*	*51*	*103*
Birth ≥10 months after dx	*82*	*91*	*150*	*323*

[a] Because subjects were linked to birth certificates for the same and subsequent years as their diagnosis, the total births identified from the linkage includes those occurring after diagnosis, as well as those that occurred during the same calendar year prior to diagnosis.

The number of women with births identified in the birth certificates includes 141 in Seattle; 225 in Detroit; and 278 in Los Angeles, representing approximately 3%-5% of the total women with breast cancer (Table 1). This proportion is slightly lower than that predicted based on the preliminary linkage conducted in Seattle prior to this project and is the result of several factors. First, the preliminary linkage was conducted as an unfunded activity without any refinement and included all possible linkages as a result of the file merge. In the present study, criteria were established to refine the accuracy of the linkage and several potential linkages were reviewed and discarded as inaccurate. Second, in the preliminary linkage a woman with multiple primary tumors may have had more than one registry record, inflating the number of birth record linkages. In the present study, programming resources were available to eliminate these "duplicate" records prior to linkage. Finally, linkages were further refined in the present study based on dates of the birth (on the birth certificate) and dates of diagnosis (from the Registry). Because a year of Registry data was linked to that same year and subsequent years of birth certificate data, some of the resultant linkages represent births that occurred during the same year, but prior to, the breast cancer diagnosis. These were excluded. The number of women with births occurring after their diagnoses of breast cancer in each region are 104 in Seattle (82 occurring 10 months or longer after diagnosis); 121 in Detroit (91 occurring 10 months or longer after diagnosis); and 201 (150 occurring 10 months or longer after diagnosis). Because of previous evidence that survival among women with pregnancy-related breast cancer diagnosis (diagnoses made while pregnant) is lower than among those with non-pregnancy related breast cancer diagnoses [Lethaby, et.al., 1996; Anderson, et., al., 1996] data will be analyzed for these groups separately.

III.B. Characteristics of women with subsequent births at each site

The mean age of breast cancer patients who subsequently gave birth was approximately 32 years of age (Table 2). Nearly half of these women were diagnosed with invasive breast cancer during the years 1985-1989, and 57%-63% had local stage disease at diagnosis, with approximately another third diagnosed with regional disease. Relatively few (ranging from 2% in Seattle to 5% in Los Angeles) had distant stage disease. Approximately 17% of subjects in all regions were Black (4% in Seattle; 34% in Detroit; 14% in Los Angeles), and 4% were of Asian ethnic groups or countries of origin (Japanese, Chinese, Korean, Vietnamese).

Table 2: Demographic & disease characteristics of breast cancer cases with births after diagnosis

	Seattle		Detroit		Los Angeles		All Regions	
	n=104		n=121		n=201		n=426	
Mean age at diagnosis (years)	31.8		31.0		32.3		31.8	
Diagnosis year	n	%	n	%	n	%	n	%
80-84	30	28.8	36	29.7	63	31.3	129	30.3
85-89	45	43.3	52	43.0	95	47.3	192	45.1
90-94	29	27.9	33	27.3	43	21.4	105	24.6
Stage of disease								
local	65	62.5	74	61.2	115	57.2	254	59.6
regional	36	34.6	42	34.7	66	32.8	144	33.8
distant	2	1.9	2	1.6	9	4.5	13	3.1
unknown	1	1.0	3	2.5	11	5.5	15	3.5
Race/ethnicity								
white	95	91.3	79	65.3	146	72.6	320	75.1
black	4	3.9	41	33.9	29	14.4	74	17.4
Asian	4	3.8	1	0.8	13	6.5	18	4.2
other	0	0.0	0	0.0	7	3.5	7	1.6
unknown	1	1.0	0	0.0	6	3.0	7	1.6

III.C. Characteristics of women with and without births ≥ 10months after diagnosis identified in birth certificates

Identification of matched comparison subjects using the revised matching program resulted in a mean of 6 comparison subjects for each exposed woman, with a maximum of 12 comparison subjects per exposed woman. Comparison subjects were not identified by the matching program for a small number of exposed women in each region (7 in Seattle; 10 in Detroit; 24 in Los Angeles). This occurred most often because these women had relatively unusual characteristics, for example, some were very young women from race/ethnic groups containing few potential comparison subjects for the close matching required by the program. In Seattle, comparison subjects were identified for all 7 of these women by relaxing some of the matching criteria (i.e., in one instance, a Vietnamese woman was matched to a non-Vietnamese women from another Asian subgroup). The decisions made in identifying these subjects were distributed to all investigators for review and approval. Detroit is currently conducting a similar procedure to identify matched comparison subjects for exposed women from that region, and Los Angeles will begin this process within the month.

Characteristics of women with births and their matched comparison subjects without births identified in the birth certificates in each region are shown in Tables 3a-3c. These are preliminary tables currently being reviewed by each region to ensure that data were not corrupted during electronic transfer and to assess the outcome of the matching program. Because of the variable number of comparison subjects per exposed woman, and because the data are presented categorically for all variables shown (whereas the matching program did not select subjects within categories for all variables), a strict correspondence between the proportions of subjects within each category for exposed and unexposed women would not be expected. However, these tables describe the two populations in general terms and serve as a basis for further refinement.

Table 3a - Characteristics of women with and without births ≥10 months after diagnosis in Seattle study region

	Seattle Region Subject Group			
	women w/ birth n=82		women w/o birth n=526	
	n	%	n	%
age at diagnosis				
<25	3	3.7	2	0.4
25-29	24	29.3	44	8.4
30-34	38	46.3	274	52.1
35-39	15	18.3	181	34.4
40-44	2	2.4	25	4.7
diagnosis year category				
80-84	26	31.7	160	30.4
85-89	37	45.1	237	45.1
90-94	19	23.2	129	24.5
stage				
local	55	67.1	348	66.2
regional	26	31.7	177	33.6
distant	0	0.0	0	0.0
unknown	1	1.2	1	0.2
race				
white	76	92.7	517	98.3
black	4	4.9	7	1.3
Asian	2	2.4	2	0.4
other	0	0.0	0	0.0
unknown	0	0.0	0	0.0
multiple primaries				
none or after dx and after cases' birth	81	98.8	525	99.8
before birth and before dx	0	0.0	0	0.0
after dx but before cases' birth	1	1.2	1	0.2
vital status at most recent follow up				
alive	70	85.4	415	78.9
dead	12	14.6	111	21.1

Table 3b - Characteristics of women with and without births ≥10 months after diagnosis in Detroit study region

	Detroit Region Subject Group			
	women w/ birth n=91		women w/o birth n=550	
	n	%	n	%
age at diagnosis				
<25	6	6.6	1	0.2
25-29	30	32.9	78	14.2
30-34	34	37.4	219	39.8
35-39	17	18.7	195	35.4
40-44	4	4.4	57	10.4
diagnosis year category				
80-84	28	30.8	169	30.7
85-89	42	46.1	242	44.0
90-94	21	23.1	139	25.3
stage				
local	59	64.8	380	69.1
regional	29	31.9	169	30.7
distant	1	1.1	0	0.0
unknown	2	2.2	1	0.2
race				
white	61	67.0	399	72.6
black	30	33.0	151	27.4
Asian	0	0.0	0	0.0
other	0	0.0	0	0.0
unknown	0	0.0	0	0.0
multiple primaries				
none or after dx and after cases' birth	89	97.8	550	100.0
before birth and before dx	2	2.2	0	0.0
after dx but before cases' birth	0	0.0	0	0.0
vital status at most recent follow up				
alive	77	84.6	423	76.9
dead	14	15.4	127	23.1

Table 3c - Characteristics of women with and without births ≥10 months after diagnosis in Los Angeles region

	Los Angeles Region Subject Group			
	women w/ birth n=150		women w/o birth n=941	
	n	%	n	%
age at diagnosis				
<25	4	2.7	1	0.1
25-29	38	25.3	73	7.8
30-34	74	49.3	484	51.4
35-39	30	20.0	344	36.6
40-44	4	2.7	39	4.1
diagnosis year category				
80-84	55	36.7	411	43.7
85-89	75	50.0	401	42.6
90-94	20	13.3	129	13.7
stage				
local	95	63.3	610	64.8
regional	46	30.7	302	32.1
distant	1	0.7	1	0.1
unknown	8	5.3	28	3.0
race				
white	101	67.3	793	84.3
black	24	16.0	96	10.2
Asian	13	8.7	16	1.6
other	6	4.0	12	1.3
unknown	6	4.0	24	2.6
multiple primaries				
none or after dx and after cases' birth	143	95.3	941	100.0
before birth and before dx	0	0.0	0	0.0
after dx but before cases' birth	7	4.7	0	0.0
vital status at most recent follow up				
alive	124	82.7	745	79.2
dead	26	17.3	196	20.8

Table 3d - Characteristics of women with and without births ≥10 months after diagnosis in all regions

	All Regions Subject Group			
	women w/ birth n=323		women w/o birth n=2017	
	n	%	n	%
region				
Seattle	82	25.4	526	26.1
Detroit	91	28.2	550	27.3
Los Angeles	150	46.4	941	46.6
age at diagnosis				
<25	13	4.0	4	0.2
25-29	92	28.5	195	9.7
30-34	146	45.2	977	48.4
35-39	62	19.2	720	35.7
40-44	10	3.1	121	6.0
diagnosis year category				
80-84	109	33.7	740	36.7
85-89	154	47.7	880	43.6
90-94	60	18.6	397	19.7
stage				
local	209	64.7	1338	66.3
regional	101	31.3	648	32.1
distant	2	0.6	1	0.1
unknown	11	3.4	30	1.5
race				
white	238	73.7	1709	84.7
black	58	17.9	254	12.6
Asian	15	4.6	18	0.9
other	6	1.9	12	0.6
unknown	6	1.9	24	1.2
multiple primaries				
none or after dx and after cases' birth	313	96.9	2016	99.9
before birth and before dx	2	0.6	0	0.0
after dx but before cases' birth	8	2.5	1	0.1
vital status at most recent follow up				
alive	271	83.9	1583	78.5
dead	52	16.1	434	21.5

Per vital status at most recent follow up from each registry, a slightly greater proportion of women with subsequent births were alive at most recent follow up (84%) than of women without subsequent births (79%). This information is currently being updated at all registries using the methods described earlier in this report, and thus no conclusions concerning survival can be drawn at this time. When vital status updates are completed at all registries, and this information is merged with the analysis database so that most recent information available is used, further analyses will be conducted. Estimates of the relative risk of dying and 95% confidence intervals associated with a woman's status concerning the occurrence of births subsequent to breast cancer diagnosis will be derived using Cox proportional hazards regression. This will be conducted using either the EGRET or STATA statistical packages. In these analyses, age of diagnosis will be controlled for as a continuous variable. Stage of disease at diagnosis, race/ethnicity, year of diagnosis, and presence of prior multiple primary tumors (the matching variables) will also be controlled. Cumulative survival of women with and without births will be measured with left truncation of survival times at the reference date (date of birth or same date for matched comparison subjects) since women were required to be alive at this point to be eligible for the study. Thus, we will compute the risk of dying associated with having a subsequent birth among women who had similar periods of survival after diagnosis, conditional on their having survived until reference date after diagnosis. Observations will be right censored at either the date of most recent follow-up or date of death. This technique has been used previously in similar studies [Malone, 1996].

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