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Epidemiology of Inflammatory Breast Cancer (IBC)¹

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Abstract

Inflammatory breast cancer (IBC) is a rare and aggressive form of breast cancer with unknown etiology and generally poor outcome. It is characterized by diffuse edema (*peau d'orange*) and redness (erythema), although either the disease itself or case definitions have varied over time and place, confounding temporal trends and geographic variations. In this review, we discuss case definitions for IBC and its clinical characteristics; describe its geographic variation, age and racial distribution, incidence and survival patterns, and summarize the very limited information on its epidemiologic risk factors. We also incorporate emerging data from the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) Program.

Keywords

Inflammatory breast cancer; epidemiology; etiologic factors

Case Definition for Inflammatory Breast Cancer (IBC)

IBC is an aggressive and lethal form of breast cancer. It is characterized by the clinical appearance of inflammation, with edema and redness of the breast. However, the appearance of inflammation is not due to true physiologic inflammatory response but rather due to pathologic plugging of the dermal lymphatics of the breast with tumor emboli.

This condition was first described in 1814 by Sir Charles Bell [14]; but, it was not until 1924 that the term inflammatory breast cancer was proposed by Lee and Tannebaum at the suggestion of James Ewing [56,88]. Prior to this designation, IBC was referred to as von Volkmann's or Wokmann's syndrome in pregnant women, lactation cancer, carcinoma mastitoides, mastitis carcinomatosa, acute encephaloid cancer, acute mammary carcinoma, acute mammary carcinomatosis, acute brawny cancer, acute scirrhus carcinoma, acute medullary carcinoma or carcinoma telangiectaticum [42,53,55,57,71,75,82,90,92]. In all, these expressions implied an acute and aggressive breast cancer, more of a clinical than a pathological entity, often multifocal [13,18,19,33,38,66,75,92], and occurring in young women during pregnancy or lactation [53,55,75,90].

The extent of clinical signs required for IBC has not been standardized and has varied from any edema (*peau d'orange*) and redness (erythema) to edema and redness covering the entire

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breast. Archibald Leitch in 1909 emphasized the edema of IBC [57]. He described the affected breast as well-modeled from the “artistic point of view” with no flattening, no puckering, and no asymmetrical bulging—a diffuse swelling like a hypertrophy. He considered the conjunction of symmetrical hypertrophy and *peau d'orange* (orange skin) as pathognomic for IBC. The name orange skin was meant to convey an image of minute pits, regularly spaced approximately $\frac{1}{4}$ inches apart, looking as if the skin of the breast has been “dabbed with a blunt pin”.

Haagensen emphasized the redness or erythema of IBC [45,46], although the breast may not always be a bright red but rather a mere “flush of pink”. The discoloration also may not be uniform, tending to be more prominent in the dependent parts of the breast and often mottled.

The French PEV (Poussee Evolutive) breast cancer classification system has four components [32,68,34], though only PEV2 and PEV3 would be IBC in the United States.

1. *PEV 0*: Tumor with neither observable increase in size during the past 3 months nor inflammatory signs
2. *PEV 1*: Tumor with increase in size during the past 3 months but with no inflammatory signs
3. *PEV 2*: Tumor with associated inflammatory signs (edema, redness, warmth), which involve the skin of less than half the breast surface
4. *PEV 3*: Tumor with associated inflammatory signs involving more than half the breast surface

The clinically dominant case definition for IBC has been debated for more than 100 years. Thomas Bryant in 1887 observed pathologic tumor invasion of the dermal lymphatic vessels, recognizing that lymphatic obstruction produced the clinical appearance of inflammation [22]. Taylor and Meltzer described IBC as a clinical entity, in which dermal lymphatic invasion offered “pathologic proof” [87], confirming but not denying the diagnosis. Ellis and Teitelbaum along with Saltzstein preferred the pathologic over the clinical definition for IBC [36,74], proposing the alternate phrase “dermal lymphatic carcinomatosis of the breast” [36].

Others have suggested that there may be three subtypes of IBC according to combined clinical and/or pathological features [3,18,19,61,64]: 1) ‘clin-only’ IBC or clinical inflammation without pathologic plugging of the dermal lymphatics, 2) ‘path-only’ IBC or pathologic plugging of the dermal lymphatics without clinical inflammation [74], and 3) fully developed ‘clin-path’ IBC with both clinical inflammation and pathologic involvement of the dermal lymphatics.

Indeed, many factors continue to confound the contemporary case definition for IBC, leading some investigators to suggest that IBC is not a true clinical entity but rather a subset of an advanced breast cancer continuum [54,69,89]. For example, ‘*primary*’ IBC typically presents with a short but dramatic clinical course, whereas ‘*secondary*’ IBC has been described after a long history of neglected breast cancer or with recurrent breast cancer after a non-inflammatory primary breast cancer [19,49,51,87]. IBC is most commonly associated with ductal breast carcinomas of no special type or not otherwise specified (duct NST or NOS) but has been reported with all histologic subtypes [45,72], including lobular [20,26], medullary [18,20,26,37,55–57,72,75], papillary [72], mucinous [43,72], comedocarcinoma [26], and Paget's disease [33,66,72,87]. There is no recognized precursor lesion for IBC. Indeed, with dermal lymphatic infiltration, IBC is technically *de novo* metastatic at the time of primary diagnosis.

American Joint Committee on Cancer (AJCC) case definition for IBC [1]

Currently, the most widely used case description in the United States (US) comes from the AJCC and is based upon the original description of Haagensen [45,46]. Designated TNM T4d and Stage IIIB or IV, the AJCC defines IBC as a composite clinicopathologic entity characterized clinically by diffuse edema (*peau d'orange*) and erythema of the breast, over the majority of the breast and often without an underlying mass. The clinical appearance is due to pathologic plugging of the dermal lymphatics of the breast, but pathologic involvement of the dermal lymphatics alone does not confirm the diagnosis.

Population-based case definitions for IBC

Definitions of IBC in population-based registries in the US have varied over time. With its beginning in 1973 (Table 1), the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute coded IBC according to the International Classification of Diseases for Oncology 8530 designation [15,77,86], which required pathologic plugging of the dermal lymphatics with tumor emboli. Clinical inflammation is not considered for ICD-O 8530. The National Association of Central Cancer Registries (NAACCR) also has identified IBC cases by ICD-O 8530 [93].

Although ICD-O 8530 is the most conservative IBC designation, it probably underestimates the true frequency of this disease. Starting in 1988, SEER linked extent of disease (EOD) codes to AJCC designations [76]. SEER's EOD-E 70 (1988+) corresponded to the AJCC T4d designation, i.e., "inflammatory carcinoma, including diffuse (beyond that directly overlying the tumor) dermal lymphatic permeation or infiltration." EOD-S 998 (1988+) was described as "diffuse, widespread: 3/4's or more of the breast; inflammatory breast cancer." When using a comprehensive case definition (i.e., ICD-O 8530 or EOD-E 70 or EOD-S 998), designed to capture all of the unique clinical and pathologic components of this disease from 1988 to 2002 (Table 1), the sample size for IBC cases in SEER more than doubles, i.e., from $n = 2,111$ with ICD-O 8530 alone compared to $n = 4,432$ with the comprehensive case definition.

Descriptive Data: (See Appendix for Materials and Statistical Methods)

Gender, racial, and geographic variation for IBC

In the US, the most recent population-based estimates from the large-scale NAACCR and SEER programs suggest that IBC defined pathologically (ICD-O 8530) comprises 1% and 0.59% of all newly diagnosed breast cancer cases among women and men, respectively [25, 93]. If defined comprehensively with both pathological and clinical criteria (ICD-O 8530 or EOD-E 70 or EOD-S 998), IBC comprises 1.9% (Table 2) and 1.4% of breast cancers among women and men, respectively. Using the SEER 9 Registries database during the years 1988 and 2000 and the comprehensive case definition (ICD-O 8530 or EOD-E 70 or EOD-S 998), Hance et al. found that IBC incidence rates were significantly higher among Black women (3.1 per 100,000 woman-years) than among White women (2.2 per 100,000 woman-years, $p < 0.001$) [47], which was similar to the results of Chang et al. and Wingo et al. (using the more conservative case definition for IBC, i.e., ICD-O 8530) [25,93].

Using SEER's 13 Registry Database and the comprehensive case definition for IBC (ICD-O 8530 or EOD-E 70 or EOD-S 998), we examined geographic variation among the different SEER sites in Table 3, ranked in order of decreasing age-adjusted incidence rates. Rates ranged from a high of 3.042 cases per 100,000 woman-years in the Los Angeles registry to a low of 2.064 per 100,000 woman-years in the San Jose-Monterey registry. Percent frequency distribution for IBC cases compared to all breast cancer cases decreased 39% from 2.45% in the Los Angeles Tumor Registry to a low of 1.49% in the Connecticut Tumor Registry.

In Fig. 1, age-specific incidence rate curves for SEER's registries (excluding rural Georgia and Alaska due to small sample sizes) were superimposed onto a single graph. Notwithstanding different RRs and frequency distributions among the various registries (Table 3), the graphs for all 11 SEER sites were nearly identical. Parenthetically, similarly shaped age-specific rate patterns imply that SEER's coding scheme for IBC was geographically robust among its various registries.

In other countries, the proportion of breast cancers that are IBC also varies [50], but is generally higher than in the US. At an oncology center in Spain, 2.9% of breast cancers over the period

1977–1993 were considered IBC, defined as diffuse or more than $\frac{2}{3}$ involvement of the breast with clinical inflammatory signs [3]. At the Institute Gustave Roussy in France, IBC defined as redness and edema covering more than half of the breast comprised 5.4% of breast cancers over the period 1955–1961 [84]. At this same institution and during the period 1989–1993,

IBC defined as clinical signs covering greater than $\frac{1}{3}$ of the breast, comprised 2.1% of breast cancer cases [85]. In a case series from Turkey, IBC defined as tumor in the dermal lymphatics, comprised 5% of all breast cancers [44]. IBC comprised 12% of breast cancers at a medical center in Pakistan over the period 1992–1998 based on a clinical diagnosis or pathologic diagnosis [12] and 17.5% of breast cancers in a teaching hospital in Nigeria over the period 1978–1983 based on a diagnosis of clinical signs covering more than 50% of the breast [28]. In Tunisia, estimates of PEV3 have ranged from approximately 50% for the period 1969–1974 to 6.2% in all of Tunisia during 1994 [32,65,68,84].

Age distribution at diagnosis

Median ages at diagnosis for IBC were nearly 10 years greater for men than for women ($p < 0.001$), 66.5 and 57 years, respectively [78]. Among women with IBC, median ages varied by racial group, ranging from 49.5 years for American Indian/Alaskan Natives to 54 years for Black and Asian Pacific Islanders (API) and to 58 years for Whites [47,78,93]. For women overall, median age was 57 years for IBC and 61.9 years for all breast cancer cases combined (Table 2).

Although age-specific incidence rates increase steadily or linearly for most epithelial cancers such as colorectal and lung cancer [10,11,17], this simple linear model does not apply to breast cancer overall, Figs 2–3 [16,35,62]. Unlike other solid tumors, overall age-specific rates for all breast cancers cases combined rise rapidly until age 50 years then continue to increase at a slower pace (Figs 2A and 3A), implying that key carcinogenic events occur before rather than after menopause [21,70]. The peculiar pause in the age-specific rate curve has been termed Clemmesen's hook [29]. Notably, Clemmesen's hook in rates corresponds to the dip in the bimodal age frequency distribution curve for female breast cancer overall (Figs 2B and 3B), and has been attributed to menopause [4].

In contrast to breast cancer overall, the carcinogenic process for IBC appears to be dominated by early-onset breast cancer types [6–8,47,79,80]. For example, age-specific incidence rates increase rapidly until age 50 years then flatten or fall for IBC, irrespective of ER expression or race (Figs 2A and 3A). The corresponding age frequency distribution plot confirms early age frequency distribution, irrespective of ER expression or race (Figs 2C and 3C). That is, regardless of ER positive or negative expression, White, Black, Asian and Pacific Islanders (API) races, all IBC cases are characterized by early-onset breast cancer populations with a peak frequency or mode of approximately age 50 years. To our knowledge, the age distribution for IBC among APIs has not been previously demonstrated (Fig. 3C).

Standard tumor characteristics at diagnosis (Table 2)

Tumor size was unknown for 85.2% of IBC cases, consistent with the fact that IBC often develops without an underlying mass [1]. Lymph node status, grade, and estrogen (ER) and progesterone (PR) expression in Table 2 were similar to data from Wingo et al. and Hance et al. [47,93]. Cases among women with IBC compared to all breast cases were more likely to have positive axillary lymph nodes, high tumor grade, and negative hormone receptors. For example, among breast cancers with known ER expression, ER negative tumors comprised 22.5% of all breast cancer cases (47,251 of 209,718) compared to 45.6% of IBC cases (1,654 of 3,631) [31,48,91]. Duct NST and lobular carcinomas were the most common histologic types for both IBC and all breast cancer cases, though IBC cases were observed among all histologic types.

Temporal trends

There have been two relatively recent attempts to define the temporal trends for IBC [25,47], both using the SEER database, though with different case definitions. Using the most conservative designation for IBC with dermal invasion of the lymphatic ducts (ICD-O code 8530), Chang et al. identified $n = 913$ White and $n = 121$ Black women with IBC among nearly 200,000 breast cancer cases, diagnosed during the years 1975 to 1992 [25]. During this time period, IBC rates doubled from 0.3 to 0.7 cases per 100,000 woman-years for Whites and from 0.6 to 1.1 for Blacks. Extending Chang et al.'s observations an additional 10 years with the most current SEER data for cases diagnosed during the years 1973 to 2002, Fig. 4(A) shows that IBC rates according to ICD-O 8530 increased at an annual rate of 4.35% per year (95% CI, 3.67% to 5.03%), although the figure may show a slowing of rates in the 1990s.

According to the comprehensive case definition (ICD-O 8530, EOD-E 70, and EOD-S 998), Hance et al. identified $n = 2,943$ White and $n = 463$ Black women with IBC among nearly 200,000 breast cancer cases, diagnosed during the years 1988 to 2000 [47]. During this time period, IBC rates increased approximately 25% from 2.0 to 2.5 cases per 100,000 woman-years ($p < 0.0001$) for Whites and 19% from 2.6 to 3.1 cases per 100,000 woman-years for Blacks ($p = 0.3153$). Extending Hance et al.'s observations another 2 years with the most current SEER data for cases diagnosed during the years 1988 to 2002, figure 4B shows a rising (though non-significant) trend for IBC, increasing at a rate of 1.23% per year (95% CI, -0.06% to 2.52%). During this same time period, all breast cancer cases combined also demonstrated slow but significant rise, i.e., 0.42% per year (95% CI, 0.14% to 0.71%). In sum, IBC incidence rates overall appear to have increased at least slightly during the last three decades, though more slowly during the latter years.

Clinical outcome

IBC is an aggressive and lethal form of breast cancer. Even with multimodality therapy, median overall survival among women with IBC is less than 4 years [63]. Although IBC comprised only 2.0% of all incident breast cancer cases, it accounted for 7.0% of all breast cancer-specific deaths in the SEER database during the years 1988–2000 [47]. Breast cancer survival among IBC patients improved modestly throughout the 1990's; however, the median survival time in Black IBC patients was only 2.0 years, compared to 3.0 years in White IBC patients according to Hance et al., during the years 1988–2000 ($P < 0.001$) [47].

Survival analyses have not been consistent among IBC subtypes, i.e., clin-only, path-only, or clin-path IBC; therefore, the clinical relevance of these sub-types is not certain. For example, SEER patients with clin-path IBC had longer survival than patients with either clin-only or path-only IBC ($p = 0.058$) [47]. In contrast, Levine et al. noted shorter 3-year relative survival rates for clin-path than for clin-only IBC [61]. Amparo noted shorter survival for clin-path than for either clin-only or path-only IBC [3]. Lucas and Perez-Mesa ranked survival in decreasing

order from path-only to clin-path to clin-only IBC [64]. Bonnier saw no difference in either disease-free or overall survival for path-only compared to clin-path IBC [18,19].

Using SEER data for 1988–2002, we reassessed cumulative breast cancer-specific survival curves with both the Kaplan Meier and smoothed cubic spline methods for all breast cancer cases combined and for IBC, according to SEER's comprehensive case definition (Table 1, Fig. 5(A) and (C); statistical methods are described in the Appendix). Five years after breast cancer diagnosis, actuarial survival for all breast cancer cases was 91.0% for ER positive tumors (95% CI, 90.8% to 91.2%) and 77.0% for ER negative lesions (95% CI, 76.6% to 77.5%). In contrast, survival for IBC cases was 48.5% for ER positive cases (95% CI, 45.2% to 52.1%) and 25.3% for ER negative cases (95% CI, 22.1% to 28.5%). In previous studies, actuarial survival for IBC was also significantly worse than survival for locally advanced non-inflammatory breast cancers [7,8].

The hazard rates in Fig. 5(B) and (D) complement the Kaplan Meier plots in Fig. 5(A) and (C). In brief, the hazard function produced a conditional rate of breast cancer death in a specified time interval following breast cancer diagnosis given that the subject was alive at the beginning of that time interval. Hazard plots illustrated that the greatest risk for breast cancer death occurred approximately 1 to 2 years following breast cancer diagnosis for all breast cancer cases as well as for IBC (Fig. 5B and D, respectively). However, IBC has an enormous hazard rate of 52.7% per year among women with ER negative tumors in the 12th month following breast cancer diagnosis, compared to the peak of 7.5% per year for all breast cancer cases in the 17th month after diagnosis. Notably, 6 to 7 years following IBC diagnosis, the hazard rate for breast cancer death is no greater for ER negative than for ER positive tumors.

Analytic Data

Perhaps due to its rarity, there are few analytic case-control or case-case epidemiologic studies regarding IBC. The etiology of IBC has been examined in one case-case study of 68 IBC cases in the United States [24] and one case-case study in Pakistan [12]. The etiology of rapidly progressing breast cancer, which encompasses IBC as well as milder forms of the disease, has also been studied in case-comparison studies conducted in Tunisia in the 1970s and 1980s [58,59,67,68,83]. Information on associated factors is also available from case series. Due to sparse data, none of the results are definitive.

Menstrual factors

Although IBC is diagnosed at younger ages on average than non-IBC, premenopausal status has not been consistently associated with IBC. In an analysis of 68 IBC cases and 143 non-IBC cases from the M.D. Anderson Cancer Center in the United States, 49% of IBC cases versus 39 percent of non-IBC cases were premenopausal at diagnosis. After controlling for age and body mass index, the odds ratio (OR) for IBC associated with being menopausal was 0.37 (95% CI 0.15–0.89) [24]. Among cases of rapidly progressing breast cancer in Tunisia (of which 83% were classified as PEV3 with signs of redness and edema over more than half of the breast), 52.5% of premenopausal patients and 57% of postmenopausal patients were PEV + [68]. In a Nigerian case series, 72% of PEV+ patients were premenopausal as opposed to 70% of non-PEV patients [28]. In a case-case study of inflammatory breast cancer in Pakistan based on 40 IBC cases and 80 non-IBC cases identified from 1992 to 1998, there were no major differences in menopausal status among the case groups [12].

Age at menarche has also not been consistently associated with IBC. In a case-comparison study conducted in the United States [24], IBC cases had a slightly earlier age at menarche than non-IBC cases (12.2 vs. 12.7 years), but this difference was not statistically significant and was not associated with risk in multivariable analyses. In the Tunisian studies of rapidly

progressing breast cancer, earlier age at menarche was not a risk factor for PEV+ tumors in premenopausal women, but a later age at menarche was associated with PEV+ tumors in postmenopausal women [68].

Reproductive factors

Many reports have noted that IBC is associated with pregnancy and/or lactation [27,37,53, 55,68,75,90], whereas other series suggest that IBC is no more common for pregnancy-related tumors than for other breast cancer types [52,66,82]. In their classic description of IBC in 1924 [56], Lee and Tannenbaum did not find a single IBC case during pregnancy. However, $n = 14$ of their 28 IBC cases (or 50%) occurred after lactation. Reviewing $n = 92$ records from the Memorial and Pondville Hospitals in New York along with $n = 113$ cases from the medical literature, Taylor and Meltzer reported that 21% ($n = 45$ of 205) of breast cancer cases occurring in association with pregnancy or lactation were of the “inflammatory type” [87]. To them it seemed “apparent that the structure of the breast late in pregnancy and/or during lactation favored the development of IBC.”

In a more recent case-control study designed to assess the influence of pregnancy on breast cancer outcome [20], Bonnier et al. compared $n = 154$ patients presenting with pregnancy-related breast cancer with a control group of $n = 308$ patients presenting with non-pregnancy-associated breast cancer, treated in 23 French hospitals during the years 1960 to 1993. Non-pregnancy associated cases were matched to pregnancy associated cases with regard to age at diagnosis and the beginning date of treatment. There were 40 of 154 (26%) cases of IBC in the pregnancy group compared to 28 of 308 (9.1%) in the non-pregnancy group ($p < 0.00001$). IBC was defined according to the criteria of Haagensen and/or the presence of tumor emboli in the dermal lymphatics [18,45]. In analyses of rapidly progressing breast cancer in Tunisia, 30% of the PEV+ tumors in premenopausal women were associated with pregnancy (defined as breast cancer occurring in a woman who was either pregnant or lactating at the time of discovery of the tumor) versus 13% of the PEV- tumors [68]. There was no association of PEV+ tumors with pregnancy in postmenopausal women. In a study of breast cancer cases in Nigeria identified between 1978 and 1993, 2.6% of 39 PEV+ patients were pregnant versus 4.9% of 81 non-PEV patients [28]. However, 10.3% of PEV+ patients were lactating versus 4.9% of non-PEV patients.

Tabbane et al. also evaluated the roles of pregnancy and lactation in breast cancer among young women in the Salah-Azaiz Institute of Tunis [83]. They compared two age groups for cases diagnosed during the years 1973 to 1980: patients under age 30 years (Group A, $n = 48$) and cases between ages 45 and 49 (Group B, $n = 160$). In IBC defined by the PEV criteria, pregnancy, and lactation were more frequent among women under the age of 30 compared to women age 45 to 49 years, although these associations did not reach statistical significance. Notably, nearly all breast cancer cases associated with pregnancy or lactation were of the inflammatory type.

Chang et al. noted that 88% of IBC cases and 89% of non-IBC cases had ever been pregnant [24]. Patients with IBC were somewhat younger at first birth (21.2 yrs) than non-IBC cases (23.0 yrs), but this difference was not statistically significant and in multivariable analyses this factor was not associated with increased risk. In a case-case study in Pakistan, the mean age at first live birth was somewhat younger in IBC cases than non-IBC cases (17 versus 19 years), but it was not reported whether this difference was statistically significant [12]. In the Tunisian studies of rapidly progressing breast cancer, age at first pregnancy was not examined in premenopausal women because a large subset of women did not report the information, but this variable was not associated with PEV+ tumors in post-menopausal women. There were also no significant associations between number of live births and PEV+ tumors in either pre- or post-menopausal women.

Body mass index

Given the hypothesis that a high body mass index (BMI) is associated with a decreased risk for premenopausal and an increased risk for postmenopausal breast cancer [30], Chang and colleagues investigated whether high BMI was a risk factor for IBC [24]. Sixty-eight ($n = 68$) 'histologically-confirmed' (ICD-O 8530) IBC patients treated at the University of Texas' M.D. Anderson Cancer Clinic during the years 1985 to 1996 were pair-matched with $n = 143$ non-IBC breast cancer and $n = 134$ non-breast cancer patients, according to date of diagnosis and race. The highest BMI tertile ($\text{BMI} > 26.65 \text{ kg/m}^2$) was associated with an increased risk for IBC compared to non-IBC (Odds ratio = 2.45, 95% confidence interval = 1.05–5.73), irrespective of menopausal status, age at menarche, family history of breast cancer, gravidity, smoking status, or alcohol use.

Smoking, alcohol, family history of breast cancer, and oral contraceptive use

In an analysis of 68 IBC cases in the United States and 134 non-breast cancer cases, former smokers were at significantly lower risk than non-smokers (OR = 0.32; 95% CI, 0.14, 0.70). Current smokers were also at lower risk, but not significantly so (0.81 (95% CI 0.33–1.96) [24]. Alcohol use was not associated with risk of IBC in this study [24]. Thirteen percent of IBC cases reported a family history of breast cancer versus 8% of the non-IBC cases, but this difference was not statistically significant [24]. In a case-case study of inflammatory breast cancer in Pakistan based on 40 IBC cases and 80 non-IBC cases identified from 1992 to 1998, a positive family history for breast cancer was significantly more common in IBC than non-IBC cases (20% versus 5%) [12]. In one study there was no marked difference in oral contraceptive use between IBC cases and non-IBC cases (70% versus 72%) [24].

Area of residence and blood type

Rural residence was associated with rapidly progressing breast cancer in both pre- and post-menopausal women in Tunisia [68]. In addition, a higher proportion of PEV+ than PEV- cases had blood type A, although these differences did not quite reach statistical significance ($p = 0.07$ and $p = 0.08$ in pre and post-menopausal women, respectively). Blood group antigens are the major allogenic antigens on most epithelial cell types [39]. Blood type A has been associated more generally with increased cancer risk [41]. It is also recognized that blood group carbohydrates expressed on the cell surface of metastatic cells function as cell adhesion molecules [40].

Immunologic factors

Immunologic factors have also been examined in the Tunisian studies with regard to rapidly progressing breast cancer. Delayed hypersensitivity studies using microbial antigens and in vitro studies including lymphocyte transformation tests and measurements of B and T cells indicated that cases with rapid progression and IBC-like symptoms had an immune response comparable to that of other breast cancer patients, suggesting that rapidly progressing breast cancer is not a reflection of immunodeficiency [59]. In fact, a greater reaction to breast-tumor-related antigens was elicited in breast cancer patients with IBC-like symptoms than in other breast cancer patients [67], suggesting a hyperimmune response in those with rapidly progressing breast cancer. It is notable that other evidence also suggests that the immune response may facilitate breast cancer development. This includes evidence of low incidence of breast cancer among chronically immunosuppressed patients and clinical-pathological investigations showing an association of increased intensity of lymphocytic infiltration into the tumor mass with worse prognosis [81].

Mouse Mammary Tumor Virus (MMTV)

Early studies showed no association between the inflammatory phenotype and gp52, the 52,000 dalton envelope-like protein (env) of MMTV [58]; in more recent analyses testing for the 250-bp sequence of the MMTV env gene, the percentage of env-positive tumors was 81% (13 of 16 tumors) for PEV3, 67% (4 or 6 tumors for PEV2, 90% (9 of 10 tumors) for PEV1, and 43% (3 of 7 tumors) for PEV0 [60]. Moreover, the percentage of breast cancer patients in Tunisia who were MMTV positive was significantly higher (74%) compared with breast cancer patients in the United States (36%), Italy (38%), Australia (42%), Argentina (31%), and Vietnam (0.8%).

Prognostic factors

Only a few studies have attempted to relate the presence of individual risk factors to the length of survival among IBC patients. M.D. Anderson investigators examined the influence of obesity and menopausal status at diagnosis upon IBC survival [23]. One hundred and seventy-seven ($n = 177$) IBC cases, treated during the years 1974 to 1993, were categorized as obese ($\text{BMI} \geq 30 \text{ kg/m}^2$), overweight ($25 \leq \text{BMI} < 30 \text{ kg/m}^2$), or of normal body weight ($\text{BMI} < 25 \text{ kg/m}^2$). Results suggested that menopausal status was an effect modifier of the association of obesity and IBC survival. That is, higher BMI contributed to shorter IBC survival among postmenopausal women but not among premenopausal women, who had worse survival regardless of BMI.

Conclusion

IBC is an aggressive, lethal, and relatively rare form of breast cancer with varying clinicopathological case definitions over time and space. The percentage of breast cancers considered IBC varies geographically, with lower proportions in the US (1–2%) than in other parts of the world. Incidence rates of IBC are higher in Blacks than Whites based on data from population-based registries in the United States. IBC tends to be diagnosed at significantly younger ages than non-IBC and at younger ages in Blacks and Asian/Pacific Islanders than in Whites as well as in Hispanics than non-Hispanics. It is diagnosed at older ages in men than women. Age-specific incidence rates increase until age 50 years and then flatten or fall, implying an important etiologic role for premenopausal carcinogenic events and/or exposures. Incidence rates of IBC have increased modestly over the past three decades in the United States. Survival is much worse in IBC cases than in non-IBC cases.

Sparse epidemiologic analytic data suggest an association between pregnancy/lactation and IBC. Other reproductive parameters, such as early age at menarche, premenopausal status, and late age at first live birth have not been consistently linked to IBC. Several studies link a family history of breast cancer to IBC, and one study has linked larger BMI to an increased risk in both pre- and post-menopausal women and past smoking to a reduction in risk. Studies in Tunisia from the 1970s and 1980s have linked rural residence, a hyperimmune response, and MMTV to increased risk.

Appendix (Materials and Methods)

We searched the PubMed database of the National Library of Medicine for articles concerning the epidemiology of IBC. Perhaps due to its rarity, there were few analytic (case-control) studies regarding etiologic risk factors for IBC. Moreover, many descriptive reports were derived from relatively small case series, using frequency (or percent) rather than age-adjusted rate data. So, the population-based characteristics of this disease have been difficult to establish.

Large-scale population-based datasets such as the SEER program provided age-adjusted descriptive data for IBC, but these databases are not without their own set of problems. Most importantly, there are no centralized laboratories or histopathologic slide review for diagnostic confirmation. Consequently, these databases could be affected by differential misclassification or detection rates, incomplete or non-standardized data. However, in theory, these population-based programs should balance diagnostic and geographic variation within their catchment areas, reflecting actual pathologic or clinical practices and provide real world estimates for IBC [6]. We, therefore, have supplemented this review with emerging data from the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) program (November 2004 submission) [78].

Population-based incidence data

Incidence rates with standard errors (*SE*) were calculated using SEER*Stat 6.1.4, age-adjusted to the 2000 US standard, and then expressed per 100,000 person-years. Relative risks for tumor characteristics were expressed as incidence rate ratios (RRs), where a given characteristic was compared to a referent characteristic with an assigned RR of 1.0. Age-specific incidence rate curves were charted on a log-log scale [10,11]. Probability density function curves for age at diagnosis were plotted, as previously described [5,9]. In brief, density function plots reflect smoothed estimates of frequency histograms by age at diagnosis, where density $\times 100 =$ percentage.

Survival methods

We used a flexible cubic spline smoothing method to estimate both the hazard function and the survival function of breast cancer-specific death following the breast cancer diagnosis [73]. We calculated the hazard function for breast cancer mortality using a smoothed cubic spline curve that maximizes the likelihood function of the observed time-to-event data. The nodes of cubic spline were selected using Akaike's Information Criteria (AIC) [2]. We also constructed the 95% confidence intervals (95% CIs) for both curves, using a bootstrap resampling method.

The hazard function was defined as the instantaneous rate of breast cancer death in a specified time interval following breast cancer diagnosis, given that the subject was alive at the beginning of that time interval. The cubic spline hazard function described the rate of failure as a continuous function over time. Both the hazard and survival functions of breast cancer death were plotted on the y-axis, and the time following breast cancer diagnosis was plotted on the x-axis. The 95% CIs for both the hazard and survival curves were plotted in the same figure.

References

1. Greene, FL.; Page, DL.; Fleming, ID.; Fritz, AG.; Balch, CM.; Haller, DG.; Morrow, M., editors. AJCC. AJCC Cancer Staging Handbook. Springer; New York: 2002. p. 255-281.
2. Akaike, H. 2nd International Symposium on Information Theory. Petrov, BN.; Csaki, F., editors. Budapest: Akademiai Kiado; 1973. p. 267-281.
3. Amparo RS, Angel CD, Ana LH, Antonio LC, Vicente MS, Carlos FM, Vicente GP. Inflammatory breast carcinoma: pathological or clinical entity? Breast Cancer Res Treat 2000;64:269–273. [PubMed: 11200777]
4. Anderson E, Reed SC, Huseby RA, Oliver CP. Possible relationship between menopause and age at onset of breast cancer. Cancer 1950;3:410–414. [PubMed: 15414462]
5. Anderson WF, Chatterjee N, Ershler WB, Brawley OW. Estrogen receptor breast cancer phenotypes in the surveillance, epidemiology, and end results database. Breast Cancer Res Treat 2002;76:27–36. [PubMed: 12408373]

6. Anderson WF, Chu KC, Chang S, Sherman ME. Comparison of age-specific incidence rate patterns for different histopathologic types of breast carcinoma. *Cancer Epidemiol Biomarkers Prev* 2004;13:1128–1135. [PubMed: 15247123]
7. Anderson WF, Chu KC, Chang S. Inflammatory breast carcinoma and non-inflammatory locally advanced breast carcinoma: distinct clinicopathologic entities? *J Clin Oncol* 2003;21:2254–2259. [PubMed: 12805323]
8. Anderson WF, Chu KC, Chang S. Inflammatory breast carcinoma: the sphinx of breast cancer research. *J Clin Oncol* 2004;22:381–384. reply. [PubMed: 14722054]
9. Anderson WF, Chu KC, Chatterjee N, Brawley OW, Brinton LA. Tumor variants by hormone receptor expression in white patients with node-negative breast cancer from the Surveillance, Epidemiology, and End Results database. *J Clin Oncol* 2001;19:18–27. [PubMed: 11134191]
10. Armitage P, Doll R. A two-stage theory of carcinogenesis in relation to the age distribution of human cancer. *Br J Cancer* 1957;11:161–169. [PubMed: 13460138]
11. Armitage P, Doll R. The age distribution of cancer and a multi-stage theory of carcinogenesis. *Br J Cancer* 1954;8:1–12. [PubMed: 13172380]
12. Aziz SA, Pervez S, Khan S, Kayani N, Azam SI, Rahbar MH. Case control study of prognostic markers and disease outcome in inflammatory carcinoma breast: a unique clinical experience. *Breast J* 2001;7:398–404. [PubMed: 11843851]
13. Barber KW, Dockerty MB. Inflammatory carcinoma of the breast. *Surg Gynecol Obstet* 1961;112:406–410. [PubMed: 13686772]
14. Bell, C. *A System of Operative Surgery founded on the Basis of Anatomy*. Hale and Hosmer; Hartford, CT: 1816.
15. Berg JW, Hutter RV. Breast cancer. *Cancer* 1995;75:257–269. [PubMed: 8001000]
16. Bernards R, Weinberg RA. Metastasis genes: A progression puzzle. *Nature* 2002;418:823. [PubMed: 12192390]
17. Bertram JS. The molecular biology of cancer. *Mol Aspects Med* 2000;21:167–223. [PubMed: 11173079]
18. Bonnier P, Charpin C, Lejeune C, Romain S, Tubiana N, Beedassy B, Martin PM, Serment H, Piana L. Inflammatory carcinomas of the breast: a clinical, pathological, or a clinical and pathological definition? *Int J Cancer* 1995;62:382–385. [PubMed: 7635562]
19. Bonnier P, Piana L, Khouzami A, Romain S, Padata J, Charpin C, Vacheret H, Jacquemier J, Tubiana N, Lejeune C, et al. Inflammatory carcinoma of the breast. *Eur J Gynaecol Oncol* 1992;13:7–11. [PubMed: 1511718]
20. Bonnier P, Romain S, Dilhuydy JM, Bonichon F, Julien JP, Charpin C, Lejeune C, Martin PM, Piana L. Influence of pregnancy on the outcome of breast cancer: a case-control study. *Societe Francaise de Senologie et de Pathologie Mammaire Study Group. Int J Cancer* 1997;72:720–727. [PubMed: 9311584]
21. Brinton, LA.; Lacey, J.; Devesa, SS. *Cancer of the Breast*. Donegan, WL.; Spratt, JS., editors. Saunders; Philadelphia: 2002. p. 111–132.
22. Bryant, T. *Diseases of the Breast*. Cassell & Company, Limited; London, Paris, New York & Melbourne: 1887. p. 186–194.
23. Chang S, Alderfer JR, Asmar L, Buzdar AU. Inflammatory breast cancer survival: the role of obesity and menopausal status at diagnosis. *Breast Cancer Res Treat* 2000;64:157–163. [PubMed: 11194451]
24. Chang S, Buzdar AU, Hursting SD. Inflammatory breast cancer and body mass index. *J Clin Oncol* 1998;16:3731–3735. [PubMed: 9850015]
25. Chang S, Parker SL, Pham T, Buzdar AU, Hursting SD. Inflammatory breast carcinoma incidence and survival: the surveillance, epidemiology, and end results program of the National Cancer Institute, 1975–1992. *Cancer* 1998;82:2366–2372. [PubMed: 9635529]
26. Charpin C, Bonnier P, Khouzami A, Vacheret H, Andrac L, Lavaut MN, Allasia C, Piana L. Inflammatory breast carcinoma: an immunohistochemical study using monoclonal anti-pHER-2/neu, pS2, cathepsin, ER and PR. *Anticancer Res* 1992;12:591–597. [PubMed: 1352440]
27. Chiedozi LC. Prognostic significance of exclusive skeletal metastases in stage IV primary carcinoma of the breast. *Surg Gynecol Obstet* 1988;167:303–306. [PubMed: 3420504]

28. Chiedozi LC. Rapidly progressing breast cancer in Nigeria. *Eur J Surg Oncol* 1987;13:505–509. [PubMed: 3691823]
29. Clemmesen J. Carcinoma of the breast. *Br J Rad* 1948;21:583–590.
30. Colditz GA, Rosner B. Cumulative risk of breast cancer to age 70 years according to risk factor status: data from the Nurses' Health Study. *Am J Epidemiol* 2000;152:950–964. [PubMed: 11092437]
31. Contesso G, May-Levin F, Delarue JC, Mouriesse H, Sancho-Garnier H, Lemaout M. Inflammatory tumors of the human breast: determination of estrogen and progesterone receptors. *Recent Results Cancer Res* 1984;91:157–162. [PubMed: 6729212]
32. Costa J, Webber BL, Levine PH, Muenz L, O'Connor GT, Tabbane F, Belhassen S, Kamaraju LS, Murali N. Histopathological features of rapidly progressing breast carcinoma in Tunisia: a study of 94 cases. *Int J Cancer* 1982;30:35–37. [PubMed: 6288578]
33. Dawson EK, Shaw JJM. Mammary cancer with generalized telangiectatic carcinoma ('carcinoma erysipelatodes'). *Br J Surg* 1937;25:100–117.
34. Denoix, P. Treatment of Malignant Breast Cancer. Springer/Verlag; Berlin: 1970.
35. Easton D. Breast cancer-not just whether but when? *Nat Genet* 2000;26:390–391. [PubMed: 11101827]
36. Ellis DL, Teitelbaum SL. Inflammatory carcinoma of the breast. A pathologic definition. *Cancer* 1974;33:1045–1047. [PubMed: 4819210]
37. Ewing, J. Neoplastic Diseases a Treatise on Tumors. W.B. Saunders Company; Philadelphia: 1934. p. 523–583.
38. Fisher ER, Sass R, Fisher B, Gregorio R, Brown R, Wickerham L. Pathologic findings from the National Surgical Adjuvant Breast Project (protocol 6). II. Relation of local breast recurrence to multicentricity. *Cancer* 1986;57:1717–1724. [PubMed: 2856856]
39. Garratty G. Blood group antigens as tumor markers, parasitic/bacterial/viral receptors, and their association with immunologically important proteins. *Immunol Invest* 1995;24:213–232. [PubMed: 7713584]
40. Glinsky GV, Ivanova AB, Welsh J, McClelland M. The role of blood group antigens in malignant progression, apoptosis resistance, and metastatic behavior. *Transfus Med Rev* 2000;14:326–350. [PubMed: 11055077]
41. Greenwell P. Blood group antigens: molecules seeking a function? *Glycoconj J* 1997;14:159–173. [PubMed: 9111133]
42. Gros C, Colin C, Haehnel P. Sex chromatin (Barr body) and inflammatory carcinoma of the breast. *Biomedicine* 1973;19:65–67. [PubMed: 4731980]
43. Guerin M, Gabillot M, Mathieu MC, Travagli JP, Spielmann M, Andrieu N, Riou G. Structure and expression of c-erbB-2 and EGF receptor genes in inflammatory and non-inflammatory breast cancer: prognostic significance. *Int J Cancer* 1989;43:201–208. [PubMed: 2563719]
44. Gunhan-Bilgen I, Ustun EE, Memis A. Inflammatory breast carcinoma: mammographic, ultrasonographic, clinical, and pathologic findings in 142 cases. *Radiology* 2002;223:829–838. [PubMed: 12034956]
45. Haagensen, CD. Diseases of the Breast. W.B. Saunders; Philadelphia: 1971. p. 576–584.
46. Haagensen, CD. Diseases of the Breast. WB Saunders; Philadelphia: 1986. p. 808–814.
47. Hance KW, Anderson WF, Devesa SS, Young HA, Levine PH. Trends in inflammatory breast carcinoma incidence and survival: the Surveillance, Epidemiology, and End Results Program at the National Cancer Institute. *J Natl Cancer Inst* 2005;97:966–975. [PubMed: 15998949]
48. Harvey HA, Lipton A, Lawrence BV, White DS, Wells SA, Blumenschein G, Lee D. Estrogen receptor status in inflammatory breast carcinoma. *J Surg Oncol* 1982;21:42–44. [PubMed: 7109635]
49. Henderson MA, McBride CM. Secondary inflammatory breast cancer: treatment options. *South Med J* 1988;81:1512–1517. [PubMed: 3201299]
50. Hotes JL, Ellison LF, Howe HL, Friesen I, Kohler B. Variation in breast cancer counts using SEER and IARC multiple primary coding rules. *Cancer Causes Control* 2004;15:185–191. [PubMed: 15017131]
51. Huston TL, Simmons RM. Inflammatory local recurrence after breast-conservation therapy for noninflammatory breast cancer. *Am J Clin Oncol* 2005;28:431–432. [PubMed: 16062091]

52. Ibrahim EM, Ezzat AA, Baloush A, Hussain ZH, Mohammed GH. Pregnancy-associated breast cancer: a case-control study in a young population with a high-fertility rate. *Med Oncol* 2000;17:293–300. [PubMed: 11114708]
53. Klotz, ID. *Uber Mastitis Carcinomatosa Gravidarum et Lactantium*. Halle; These: 1869.
54. Kokal WA, Hill LR, Poroduminsky D, Beatty JD, Kemeny MM, Riihimaki DU, Terz JJ. Inflammatory breast carcinoma: a distinct entity? *J Surg Oncol* 1985;30:152–155. [PubMed: 4079435]
55. Learmonth GE. Acute mammary carcinoma. *Can Med Assoc J* 1916;6:499–511. [PubMed: 20310801]
56. Lee BJ, Tannenbaum NE. Inflammatory carcinoma of the breast. *Surg Gynecol Obstet* 1924;39:580–595.
57. Leitch A. Peau d'orange in acute mammary carcinoma: its cause and diagnostic value. *Lancet* 1909;1:861–863.
58. Levine PH, Mesa-Tejada R, Keydar I, Tabbane F, Spiegelman S, Mourali N. Increased incidence of mouse mammary tumor virus-related antigen in Tunisian patients with breast cancer. *Int J Cancer* 1984;33:305–308. [PubMed: 6321360]
59. Levine PH, Mourali N, Tabbane F, Loon J, Terasaki P, Tsang P, Bekesi JG. Studies on the role of cellular immunity and genetics in the etiology of rapidly progressing breast cancer in Tunisia. *Int J Cancer* 1981;27:611–615. [PubMed: 6169664]
60. Levine PH, Pogo BG, Klouj A, Coronel S, Woodson K, Melana SM, Mourali N, Holland JF. Increasing evidence for a human breast carcinoma virus with geographic differences. *Cancer* 2004;101:721–726. [PubMed: 15305401]
61. Levine PH, Steinhorn SC, Ries LG, Aron JL. Inflammatory breast cancer: the experience of the surveillance, epidemiology, and end results (SEER) program. *J Natl Cancer Inst* 1985;74:291–297. [PubMed: 3856043]
62. Lilienfeld AM, Johnson EA. The age distribution in female breast and genital cancers. *Cancer* 1955;8:875–882. [PubMed: 13261037]
63. Low JA, Berman AW, Steinberg SM, Danforth DN, Lippman ME, Swain SM. Long-Term Follow-Up for Locally Advanced and Inflammatory Breast Cancer Patients Treated With Multimodality Therapy. *J Clin Oncol* 2004;22:4067–4074. [PubMed: 15483018]
64. Lucas FV, Perez-Mesa C. Inflammatory carcinoma of the breast. *Cancer* 1978;41:1595–1605. [PubMed: 639015]
65. Maalej M, Frikha H, Ben Salem S, Daoud J, Bouaouina N, Ben Abdallah M, Ben Romdhane K. Breast cancer in Tunisia: clinical and epidemiological study. *Bull Cancer* 1999;86:302–306. [PubMed: 10210765]
66. Meyer AC, Dockerty MB, Harrington SW. Inflammatory carcinoma of the breast. *Surg Gynecol Obstet* 1948;87:417–424. [PubMed: 18119795]
67. Mourali N, Levine PH, Tabbane F, Belhassen S, Bahi J, Bennaceur M, Herberman RB. Rapidly progressing breast cancer (pousse evolutive) in Tunisia: studies on delayed hypersensitivity. *Int J Cancer* 1978;22:1–3. [PubMed: 681022]
68. Mourali N, Muenz LR, Tabbane F, Belhassen S, Bahi J, Levine PH. Epidemiologic features of rapidly progressing breast cancer in Tunisia. *Cancer* 1980;46:2741–2746. [PubMed: 7448713]
69. Paradiso A, Tommasi S, Brandi M, Marzullo F, Simone G, Lorusso V, Mangia A, De Lena M. Cell kinetics and hormonal receptor status in inflammatory breast carcinoma. Comparison with locally advanced disease. *Cancer* 1989;64:1922–1927. [PubMed: 2790702]
70. Pike MC, Spicer DV, Dahmouch L, Press MF. Estrogens, progestogens, normal breast cell proliferation, and breast cancer risk. *Epidemiol Rev* 1993;15:17–35. [PubMed: 8405201]
71. Rasch C. Carcinoma erysipelatodes. *British J Derm Syph* 1931;43:351–354.
72. Robbins GF, Shah J, Rosen P, Chu F, Taylor J. Inflammatory carcinoma of the breast. *Surg Clin North Am* 1974;54:801–810. [PubMed: 4372732]
73. Rosenberg PS. Hazard function estimation using B-splines. *Biometrics* 1995;51:874–887. [PubMed: 7548706]
74. Saltzstein SL. Clinically occult inflammatory carcinoma of the breast. *Cancer* 1974;34:382–388. [PubMed: 4851056]
75. Schumann EA. A study of carcinoma mastitoides. *Ann Surg* 1911;54:69–77. [PubMed: 17862706]

76. SEER Extent of Disease – 1988 Codes and Coding Instructions. 1988. <http://seer.cancer.gov/Publications/Manuals/EOD10Dig.3rd.pdf>
77. SEER: ICD-O-3 Coding Materials. 2004. <http://seer.cancer.gov/icd-o-3/>
78. SEER: Surveillance, Epidemiology, and End Results (SEER) Program. Public-Use Database (1973–2002), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, based on the November 2004 submission. 2005. www.seer.cancer.gov
79. Stalsberg H, Thomas DB, Noonan EA. Histologic types of breast carcinoma in relation to international variation and breast cancer risk factors. WHO Collaborative Study of Neoplasia and Steroid Contraceptives. *Int J Cancer* 1989;44:399–409. [PubMed: 2777405]
80. Stalsberg H, Thomas DB. Age distribution of histologic types of breast carcinoma. *Int J Cancer* 1993;54:1–7. [PubMed: 8478135]
81. Stewart TH, Heppner GH. Immunological enhancement of breast cancer. *Parasitology* 1997;115 (Suppl):S141–S153. [PubMed: 9571699]
82. Swain SM, Lippman ME. Treatment of patients with inflammatory breast cancer. *Important Adv Oncol* 1989;129–150. [PubMed: 2651284]
83. Tabbane F, el May A, Hachiche M, Bahi J, Jaziri M, Cammoun M, Mourali N. Breast cancer in women under 30 years of age. *Breast Cancer Res Treat* 1985;6:137–144. [PubMed: 4052640]
84. Tabbane F, Muenz L, Jaziri M, Cammoun M, Belhassen S, Mourali N. Clinical and prognostic features of a rapidly progressing breast cancer in Tunisia. *Cancer* 1977;40:376–382. [PubMed: 880564]
85. Tardivon AA, Viala J, Corvellec Rudelli A, Guinebretiere JM, Vanel D. Mammographic patterns of inflammatory breast carcinoma: a retrospective study of 92 cases. *Eur J Radiol* 1997;24:124–130. [PubMed: 9097054]
86. Tavassoli, FA.; Devilee, P. Pathology and Genetics of Tumours of the Breast and Female Genital Organs. IARC Press; Lyon: 2003.
87. Taylor GW, Meltzer A. “Inflammatory carcinoma” of the breast. *Am J Cancer* 1938;33:33–49.
88. Treves N. Inflammatory carcinoma of the breast in the male patient. *Surgery* 1953;34:810–820. [PubMed: 13113500]
89. Valero V, Buzdar AU, Hortobagyi GN. Inflammatory Breast Cancer: Clinical Features And The Role Of Multimodality Therapy. *Breast J* 1996;2:345–352.
90. von Volkman, R. Beitrage zur Chirurgie. Breitkopf and Hartel; Leipzig: 1875.
91. Waldman, S.; Toonkel, LM.; Davila, E. High-Risk Breast Cancer. Ragaz; Ariel, editors. Springer-Verlag; Berlin Heidelberg: 1991.
92. Weber FP. Bilateral thoracic zosteroid spreading marginate telangiectasia-probably a variety of “carcinoma erysipelatodes” (C. Rasch)-associated with unilateral mammary carcinoma, and better termed “carcinoma telangiectaticum”. *British J Derm Syph* 1933;45:418–423.
93. Wingo PA, Jamison PM, Young JL, Gargiullo P. Population-Based Statistics for Women Diagnosed with Inflammatory Breast Cancer (United States). *Cancer Causes Control* 2004;15:321–328. [PubMed: 15090727]

Fig. 1.

Age-specific incidence rates for inflammatory breast cancer (IBC) in the Surveillance, Epidemiology, and End Results (SEER) program for 11 SEER tumor registries, i.e., Los Angeles, Utah, Atlanta (Metropolitan), New Mexico, Iowa, Hawaii, San Francisco-Oakland, Seattle (Puget-Sound), Detroit (Metropolitan), San Jose-Monterey, Connecticut.

Fig. 2.

Age distribution (rates and frequency) for all breast cancer cases combined and IBC, stratified by ER expression. a) Panel A: Age-specific incidence rates. b) Panel B: Age density plots for all breast cancer cases combined. The density function represents smoothed estimates of the age frequency distribution at diagnosis, where the density multiplied by 100 equals the percentage. c) Panel C: Age density plots for IBC.

Fig. 3. Age distribution (rates and frequency) for all breast cancer cases combined and IBC, stratified by White, Black, and Asian or Pacific Islander (API) races. a) Panel A: Age-specific incidence rates. b) Panel B: Age density plots for all breast cancer cases combined. The density function represents smoothed estimates of the age frequency distribution at diagnosis, where the density multiplied by 100 equals the percentage. c) Panel C: Age density plots for IBC.

Age-adjusted trends (1973-2002)

Age-adjusted trends (1988-2002)

Fig. 4.

Temporal trends for age-adjusted incidence rates among all breast cancer cases combined and inflammatory breast cancer (IBC) in the Surveillance, Epidemiology, and End Results (SEER) program. a) Panel A: Temporal trend for breast cancer cases diagnosed during the years 1973 to 2002. All breast cancer cases combined ($n = 420,082$) and IBC according to ICD-O 8530 ($n = 2,935$). b) Panel B: Temporal trend for breast cancer cases diagnosed during the years 1992 to 2002. All breast cancer cases combined ($n = 256,995$) and IBC according to the comprehensive SEER definition ($n = 4,432$; ICD-O 8530 or EOD-E 70 or EOD-S 998).

Fig. 5.

Survival and hazard rate plots for all breast cancer cases combined and IBC, stratified by ER expression. a) Panel A: Survival function for all breast cancer cases combined. b) Panel B: Hazard plot for all breast cancer cases combined. c) Panel C: Survival function for all breast cancer cases combined. d) Panel D: Hazard function for all breast cancer cases combined.

Rates and sample sizes among invasive female breast carcinoma cases ($n = 420,082$) in SEER's 9 Registry Database, diagnosed during the years 1973 to 2002

Table 1

YEAR at Dx	All breast Cases		Inflammatory breast cancer (IBC)									
			ICD-O 8530				EOD 70 (AJCC T4d)				EOD 998	
	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count
1973	98.481	7,187	0.454	35	0.000	0	0.0	0	0.0	0	0.0	0
1974	113.001	9,556	0.402	34	0.000	0	0.0	0	0.0	0	0.0	0
1975	105.004	9,652	0.423	40	0.000	0	0.0	0	0.0	0	0.0	0
1976	101.890	9,463	0.593	57	0.000	0	0.0	0	0.0	0	0.0	0
1977	100.777	9,499	0.402	38	0.000	0	0.0	0	0.0	0	0.0	0
1978	100.547	9,648	0.523	50	0.000	0	0.0	0	0.0	0	0.0	0
1979	102.062	10,009	0.442	41	0.000	0	0.0	0	0.0	0	0.0	0
1980	102.079	10,199	0.560	54	0.000	0	0.0	0	0.0	0	0.0	0
1981	106.294	10,764	0.492	51	0.000	0	0.0	0	0.0	0	0.0	0
1982	106.424	10,935	0.631	66	0.000	0	0.0	0	0.0	0	0.0	0
1983	111.094	11,618	0.621	65	0.000	0	0.0	0	0.0	0	0.0	0
1984	115.810	12,279	0.476	51	0.000	0	0.0	0	0.0	0	0.0	0
1985	124.075	13,357	0.712	74	0.000	0	0.0	0	0.0	0	0.0	0
1986	126.729	13,900	0.818	88	0.000	0	0.0	0	0.0	0	0.0	0
1987	134.405	15,021	0.752	80	0.000	0	0.0	0	0.0	0	0.0	0
1988	131.272	14,889	0.894	96	0.997	108	1.3	136	1.757	192	1.757	192
1989	127.149	14,628	0.706	82	1.241	142	1.5	172	2.113	242	2.113	242
1990	131.607	15,377	0.886	97	1.372	152	1.6	177	2.249	253	2.249	253
1991	133.566	15,869	0.954	110	1.508	175	1.7	204	2.382	279	2.382	279
1992	131.915	16,019	1.149	135	1.625	191	1.6	189	2.378	282	2.378	282
1993	129.136	15,963	1.133	137	1.487	179	1.4	169	2.178	266	2.178	266
1994	130.709	16,408	1.089	133	1.370	168	1.6	192	2.210	272	2.210	272
1995	132.324	16,922	1.160	148	1.543	197	1.7	215	2.326	295	2.326	295
1996	133.352	17,300	1.422	184	1.792	229	2.0	259	2.768	357	2.768	357
1997	137.356	18,181	1.328	173	1.821	238	1.9	243	2.615	343	2.615	343

YEAR at Dx	All breast Cases		Inflammatory breast cancer (IBC)					
			ICD-O 8530		EOD 70 (AJCC T4d)		EOD 998	
	Rate	Count	Rate	Count	Rate	Count	Rate	Count
1998	140.823	18,973	1.310	176	1.737	234	2.0	272
1999	140.412	19,196	1.235	167	1.691	230	2.1	283
2000	135.279	18,797	1.001	139	1.456	202	1.5	211
2001	136.629	19,345	1.309	184	1.608	227	1.9	268
2002	132.856	19,128	1.041	150	1.693	244	2.0	284
1988-2002				2,111		2,916		3,274
								4,432

Key: ICD-O, International Classification of Diseases for Oncology; EOD, SEER extent of disease; AJCC, American Joint Committee on Cancer (AJCC); Comprehensive SEER definition for IBC, IDC-O 8530 or EOD 70 or EOD 998.

Descriptive statistics among invasive female breast carcinoma cases ($n = 270,124$) in SEER's 13 Registry Database, diagnosed during the years 1992 to 2002

Table 2

	All breast cancer cases minus IBC					Comprehensive IBC				
	n	%	Rate	RR	95% CI	n	%	Rate	RR	95% CI
Frequency (n)			264,987					5,137		
% of total cases			98.1%					1.9%		
Mean age (yrs)			61.9					58.7		
Median age (yrs)			62					57		
Mean size (cm)			2.2					8.6		
Median size (cm)			1.7					9.98		
Rate (SE)			129.9 (0.3)					2.5 (0.035)		
<i>Tumor size</i>										
≤ 2.0 centimeters	151,723	56.2%	74.6	1.0	LL	102	2.0%	0.1	1.0	LL
> 2.0 centimeters	84,638	31.3%	41.4	0.6	0.5	660	12.8%	0.3	6.4	5.2
Other or unknown	28,626	10.6%	~	~	~	4,375	85.2%	~	~	~
<i>Lymph nodes</i>										
LN negative	163,153	60.4%	80.2	1.0	LL	547	10.6%	0.3	1.0	LL
LN positive	74,454	27.6%	36.8	0.5	0.5	2,850	55.5%	1.4	5.2	4.7
Other or unknown	27,380	10.1%	~	~	~	1,740	33.9%	~	~	~
<i>AJCC stage</i>										
Stage I	117,421	43.5%	57.8	1.0	LL	0	0.0%	~	~	LL
Stage II	91,777	34.0%	45.2	0.8	0.8	0	0.0%	~	~	~
Stage III	13,429	5.0%	6.6	0.1	0.1	3,724	72.5%	~	~	~
Stage IV	10,327	3.8%	5.0	0.1	0.1	1,190	23.2%	~	~	~
Other or unknown	32,033	11.9%	~	~	~	223	4.3%	~	~	~
<i>Tumor grade</i>										
Low	133,017	49.2%	65.3	1.0	LL	1,024	19.9%	0.5	1.0	LL
High	84,872	31.4%	41.7	0.6	0.6	2,865	55.8%	1.4	2.8	2.6
Other or unknown	47,098	17.4%	~	~	~	1,248	24.3%	~	~	~
<i>Pathology</i>										
Duct NST	183,740	68.0%	90.3	1.00	LL	1,429	27.8%	0.70	1.00	LL

Tubular	4,406	1.6%	2.2	0.02	0.02	0.03	1	0.0%	0.00	0.00	0.0	0.0
Lobular	21,651	8.0%	10.6	0.12	0.12	0.12	195	3.8%	0.10	0.13	0.1	0.2
Medullary	2,613	1.0%	1.3	0.01	0.01	0.01	6	0.1%	0.00	0.00	0.0	0.0
Inflammatory	0	0.0%	~	~	~	~	3,004	58.5%	1.48	2.10	2.0	2.2
Papillary	1,671	0.6%	0.8	0.01	0.01	0.01	7	0.1%	0.00	0.00	0.0	0.0
Mucinous	6,861	2.5%	3.3	0.04	0.04	0.04	20	0.4%	0.01	0.01	0.0	0.0
Paget's disease	1,999	0.7%	1.0	0.01	0.01	0.01	27	0.5%	0.01	0.02	0.0	0.0
Comedocarcinoma	4,459	1.7%	2.2	0.02	0.02	0.03	18	0.4%	0.01	0.01	0.0	0.0
Other or unknown	37,587	13.9%	~	~	~	~	430	8.4%	~	~	~	~
<i>ER</i>												
ER positive	162,467	60.1%	79.8	1.0	LL	UL	1,977	38.5%	1.0	1.0	LL	UL
ER negative	47,251	17.5%	23.3	0.3	0.3	0.3	1,654	32.2%	0.8	0.8	0.8	0.8
Other or unknown	55,269	20.5%	~	~	~	~	1,506	29.3%	~	~	~	~
<i>PR</i>												
PR positive	135,906	50.3%	66.8	1.0	LL	UL	1,611	31.4%	0.8	1.0	LL	UL
PR negative	66,878	24.8%	32.9	0.5	0.5	0.5	1,933	37.6%	1.0	1.2	1.1	1.3
Other or unknown	62,203	23.0%	~	~	~	~	1,593	31.0%	~	~	~	~

Key: Comprehensive IBC (i.e., IBC = ICD-O 8530 or EOD 70 or EOD 998); Rate, age-adjusted incidence rate expressed per 100,000 woman-years; RR, rate ratio where a given characteristic is compared to a referent value with an assigned RR of 1.0; 95% CI, 95% confidence interval with lower and upper bounds; ~, statistic not calculated; AI/AN, American Indian or Alaska Native; API, Asian or Pacific Islander; Duct NST, ductal carcinoma of no special type or not otherwise specified; ER, estrogen receptor; PR, progesterone receptor.

Table 3

Percent frequency distribution of IBC cases compared to all breast cancer cases for each SEER Tumor Registry, during the years 1992 to 2002

SEER Registry	All breast cancer cases			Comprehensive IBC				
	n	Rate	Count (n)	% of total breast cases	Rate	RR	95% CI	
Los Angeles	57,161	124.821	1,401	2.45%	3.042	1.00	LL	UL
Rural Georgia	763	2.979	21	2.75%	2.979	0.98	0.60	1.52
Atlanta (Metropolitan)	17,050	133.937	372	2.18%	2.844	0.93	0.83	1.05
Utah	10,228	115.758	233	2.28%	2.622	0.86	0.75	0.99
Iowa	24,216	129.963	459	1.90%	2.547	0.84	0.75	0.93
New Mexico	10,993	115.665	229	2.08%	2.419	0.80	0.69	0.92
Seattle (Puget Sound)	31,048	146.153	512	1.65%	2.413	0.79	0.72	0.88
San Francisco-Oakland	32,070	139.585	549	1.71%	2.392	0.79	0.71	0.87
Hawaii	8,565	126.277	148	1.73%	2.192	0.72	0.60	0.86
Detroit (Metropolitan)	31,934	134.413	515	1.61%	2.19	0.72	0.65	0.80
Alaska Natives	444	124.031	10	2.25%	2.183	0.72	0.33	1.55
Connecticut	30,128	141.093	449	1.49%	2.12	0.70	0.62	0.78
San Jose-Monterey	15,524	135.755	239	1.54%	2.064	0.68	0.59	0.78
All SEER Registries	270,124	132.429	5,137	1.90%	2.120	0.70	0.62	0.78

Key: n, sample size; Comprehensive IBC (i.e., IBC=ICD-O 8530 or EOD-E 70 or EOD-S 998); Rate, age-adjusted incidence rate expressed per 100,000 woman-years; RR, rate ratio where the rate for a given registry is compared to the Los Angeles Tumor Registry with an assigned RR of 1.00; 95% CI, 95% confidence intervals with lower and upper limits (LL and UL); ~, not calculated.