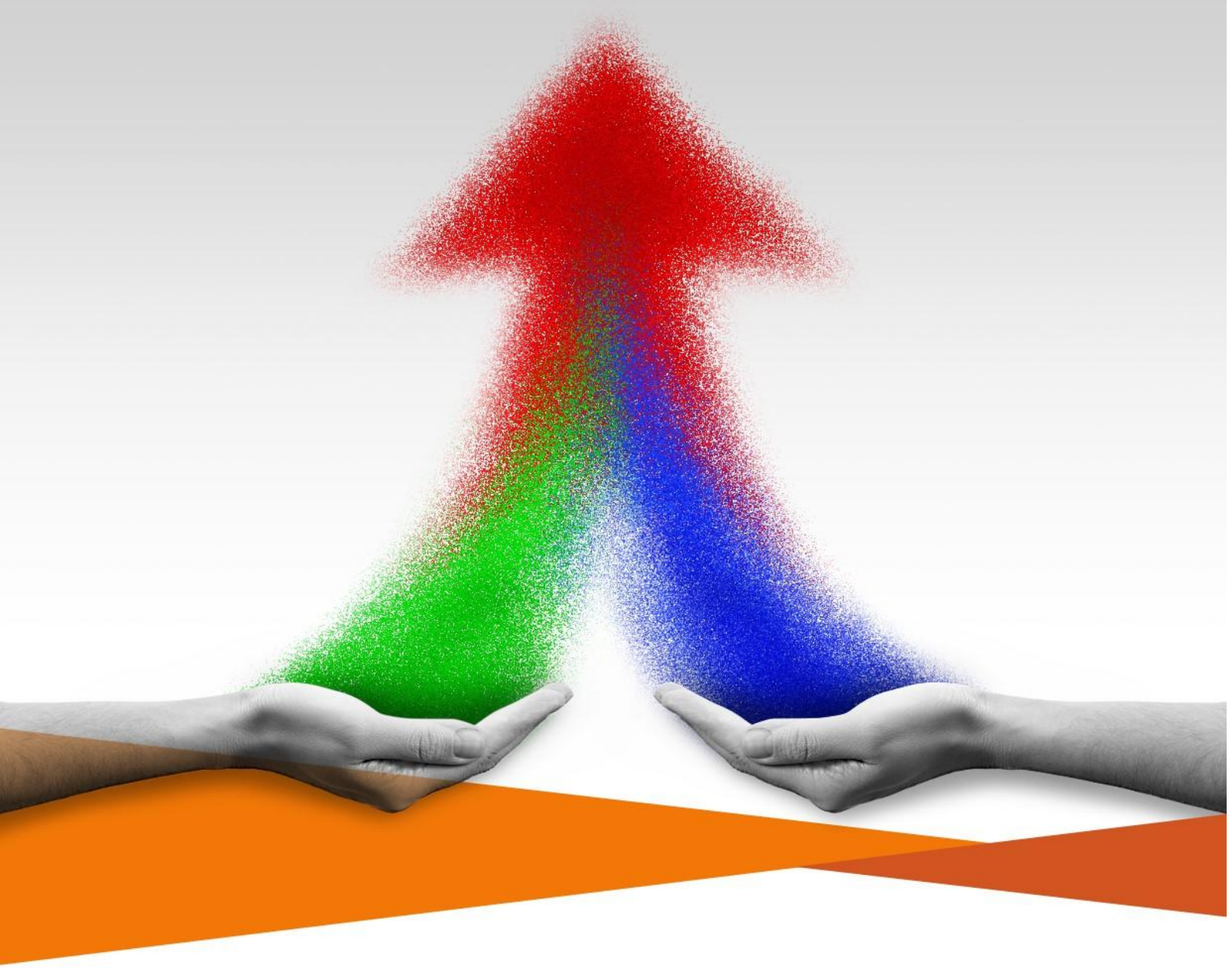

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SECOND CANCERS FOLLOWING *IN SITU* CARCINOMA OF THE BREAST

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Carcinoma *in situ* (CIS) of the breast has increased many-fold in incidence rates and as a proportion of new breast cancers following the introduction of mammographic breast screening. To provide population-based estimates of invasive breast cancer risk following CIS, we linked data on 249 incident primary CIS (median age 53 years) to the Cancer Registry of the Swiss Canton of Vaud (about 600,000 inhabitants) over the period 1977–1994. Women with concurrent invasive cancers of the breast were not included. Standardized incidence ratios (SIR) were determined according to the exact Poisson distribution, with stratification for age and year of diagnosis. A total of 24 cases of breast cancer *vs.* 3.4 expected [SIR = 7.2, 95% confidence interval (CI): 4.6–10.6], and 7 cases of other neoplasms (except non-melanomatous skin cancer) *vs.* 6.9 expected (SIR = 1.0, 95% CI: 0.4–2.1) were observed. The SIR was 10.4 during the first year, 5.6 between 1 and 4 years, and 7.7 after ≥5 years after CIS diagnosis. SIRs were consistent in women below and above age 55 years, but somewhat higher for ductal (SIR = 8.6) than lobular (SIR = 4.2) CIS. Six deaths from breast cancer were observed *vs.* 1.5 expected (standardized mortality ratio = 4.0, 95% CI: 1.5–8.7). In 13/19 ductal CIS, but in 2/4 lobular CIS, invasive cancer occurred in the same breast. In most women, CIS and subsequent invasive cancer showed the same morphological (*i.e.,* ductal or lobular) features. The cumulative risk of breast cancer was 16% 10 years after CIS diagnosis, emphasizing the importance of adequate surveillance of women after CIS of the breast. *Int. J. Cancer* 77:392–395, 1998.
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Carcinoma *in situ* (CIS) of the breast has become an increasingly important disease in North America (Ernster *et al.,* 1996) and Europe (Levi *et al.,* 1997*a*) in the last 2 decades. In the early 1990s, CIS accounted for more than 10–20% of new breast cancer cases compared to about 3% before the introduction of mammographic screening (Ernster *et al.,* 1996; Levi *et al.,* 1997*a*).

CIS includes a spectrum of lesions varying in clinical presentation, extent, growth pattern, cell type, cytonuclear differentiation and presence of necrosis (Schnitt *et al.,* 1988). Some may be hard to distinguish from benign ductal hyperplasia; in others, stromal invasion cannot be excluded. The traditional classification groups include two major groups: lobular carcinoma *in situ* (LCIS) and ductal carcinoma *in situ* (DCIS). DCIS, which arises from the ductal breast epithelium, is often clinically evident as a mass on physical examination and has a distinctive mammographic finding (microcalcifications), due to calcium deposition on central ductal necrosis (Fryckberg *et al.,* 1993).

LCIS, derived from the lobular breast epithelium, is generally considered to be a marker of increased risk of future malignancy, rather than the natural precursor of invasive disease (Fryckberg *et al.,* 1987). It lacks both clinical and mammographic signs and is, thus, mostly an incidental finding in a breast biopsy performed for other reasons (Fryckberg *et al.,* 1987).

On account of persisting uncertainty with respect to terminology (Foucar, 1996) and management (Ernster *et al.,* 1996), relatively few cohort studies (Betsill *et al.,* 1978; Page *et al.,* 1982, 1995; Habel *et al.,* 1997) have examined the ability of CIS treated only by biopsy to evolve to invasion. Herein we provide one of the first estimates of the risk of invasive breast cancer subsequent to CIS in a large population-based series coming from the Cancer Registry of the Swiss Canton of Vaud. Comparison of breast cancer risk with that of other neoplasms was also made to evaluate the potential impact of ascertainment bias.

MATERIAL AND METHODS

Data for the present report were abstracted from the Vaud Cancer Registry file, which includes incident cases of malignant neoplasms in the canton (Levi *et al.,* 1997*b*) whose population, according to the 1990 census, was about 600,000 inhabitants. The registry is tumor-based and multiple primaries occurring in one person are entered separately. Notification is based on a voluntary agreement between the recording institutions of the canton and the registry. The main sources of notification, *i.e.,* the Pathology Department, University of Lausanne, and, since the end of the 1980s, 2 private laboratories, perform over 90% of histological examinations for the population covered by the registry. Most cases are registered repeatedly and from different institutions, thus improving completeness and accuracy of registration. The basic information available from the register comprises sociodemographic characteristics of the patient (*i.e.,* age, sex), primary site and histological type of tumor according to the standard International Classification of Diseases for Oncology (ICD-O) and time of diagnostic confirmation (histological or clinical diagnosis).

Passive and active follow-up are recorded, and each subsequent item of information concerning an already registered case is used to complete the record of the patient. Information from death certificates is routinely integrated in the data file; cases known only through death certificates amount to fewer than 5% of the average number of cases registered per year. Overall histological confirmation exceeds 90%, and is 98% for breast cancer.

Since 1977, a registration scheme, applying the same standardized rules as for incident malignancies, has been implemented for CIS of the breast. In particular, all histological reports from the most important pathology laboratories were scrutinized and reviewed when reporting diagnosis of CIS. The overall incidence period considered includes years 1977–1994.

When multiple registrations of CIS were present in the same woman (n = 13), only the first was considered. After exclusion of women with (1) history of previous malignant neoplasm, with the exception of non-melanomatous skin cancer (n = 54), and (2) concurrent cancer of the breast or other sites (n = 83), our present series comprised 249 women diagnosed with histologically confirmed CIS. They included 186 DCIS (ICD-O M: 8500), 59 LCIS (ICD-O M: 8520) and 4 CIS of other or unspecified type (Table I). The age range was 27–87 years (median age 53 years).

Women with CIS were followed up to the end of 1994 for the occurrence of cancer (excluding non-melanomatous cutaneous

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TABLE I – DISTRIBUTION OF 249 WOMEN WITH CIS OF THE BREAST AND CORRESPONDING PERSON-YEARS BY AGE, HISTOLOGICAL TYPE AND YEARS SINCE DIAGNOSIS: VAUD, SWITZERLAND, 1977–94

	CIS of the breast	
	Number	Person-years
Age group (years)		
20–39	21	162
40–49	79	456
50–59	67	377
60–69	48	278
≥70	34	188
Histological type		
Ductal	186	968
Lobular	59	456
Other	4	37
Years since diagnosis		
<1	—	230
1–4	—	643
5–9	—	403
≥10	—	185
Total	249	1,461

TABLE II – OBSERVED (O) AND EXPECTED (E) NUMBERS OF CANCER AND CORRESPONDING SIRs AND 95% CIs, FOLLOWING 249 CIS OF THE BREAST BY SELECTED CHARACTERISTICS: VAUD, SWITZERLAND, 1977–1994

Characteristic	Invasive breast cancer			Other cancers[1]		
	O	E	SIR (95% CI)	O	E	SIR (95% CI)
Years since diagnosis						
<1	5	0.5	10.4 (3.3–24.2)	1	0.9	1.1 (0.0–6.1)
1–4	8	1.4	5.6 (2.4–11.0)	3	2.9	1.0 (0.2–3.0)
≥5	11	1.4	7.7 (3.8–13.7)	3	3.1	1.0 (0.2–2.8)
Age at diagnosis (years)						
<55	12	1.6	7.5 (3.9–13.2)	4	2.3	1.8 (0.5–4.5)
≥55	12	1.8	6.8 (3.5–11.9)	3	4.7	0.6 (0.1–1.9)
Histological type						
Ductal	20	2.3	8.6 (5.3–13.3)	5	5.1	1.0 (0.3–2.3)
Lobular	4	1.0	4.2 (1.1–10.7)	2	1.7	1.2 (0.1–4.2)
Total	24	3.4	7.2 (4.6–10.6)	7	6.9	1.0 (0.4–2.1)

[1]Non-melanomatous skin cancer excluded.

TABLE III – OBSERVED (O) AND EXPECTED (E) NUMBERS OF CANCERS AND CORRESPONDING SIRs AND 95% CIs, FOLLOWING 186 DCIS OF THE BREAST BY SELECTED CHARACTERISTICS: VAUD, SWITZERLAND, 1977–1994

Characteristic	Invasive breast cancer			Other cancers[1]		
	O	E	SIR (95% CI)	O	E	SIR (95% CI)
Years since diagnosis						
<1	3	0.4	8.0 (1.6–23.3)	1	0.8	1.3 (0.0–7.2)
1–4	7	1.1	6.5 (2.6–13.3)	2	2.3	0.9 (0.1–3.2)
≥5	10	0.9	11.7 (5.6–21.5)	2	2.0	1.0 (0.1–3.6)
Age at diagnosis (years)						
<55	10	0.9	11.0 (5.3–20.3)	2	1.3	1.6 (0.2–5.8)
≥55	10	1.4	7.1 (3.4–13.0)	3	3.8	0.8 (0.2–2.3)

[1]Non-melanomatous skin cancer excluded.

neoplasms), migration or death. All subsequent invasive breast cancers were considered new incident neoplasms. Overall, losses to follow-up were below 3%. A second primary cancer was defined as a new malignancy occurring in a patient notified as having had a CIS of the breast, and was classified as independent if so specified by pathological report (Levi *et al.,* 1997*b*). Histological confirmation was obtained in all subsequent primaries.

Cumulative risk was computed using the standard life table approach. Computation of expected numbers was based on site, age- and calendar year-specific incidence rates multiplied by the observed number of person-years at risk. The significance of the observed/expected ratios [standardized incidence ratios (SIR)] and the corresponding 95% confidence intervals (CI) was based on the exact Poisson distribution (Breslow and Day, 1987).

RESULTS

Table I gives the distribution of 249 women with CIS of the breast and the corresponding person-years at risk according to age, histological type and years since CIS diagnosis. Women with LCIS were on average younger (median age 50 years) than those with DCIS (median age 55 years).

Table II gives the observed and expected numbers of invasive cancer of the breast and other neoplasms in strata of selected characteristics. Overall, 24 invasive cancers of the breast were observed *vs.* 3.4 expected (SIR = 7.2, 95% CI: 4.6–10.6). The excess breast cancer risk was persistent, and of similar magnitude, across various periods since CIS diagnosis, with a SIR of 7.7 found at 5 years or more after CIS diagnosis. The same held true for age at CIS diagnosis, SIR being 7.5 below age 55 years and 6.8 at age 55 or more years. DCIS showed a SIR which was higher (8.6, 95% CI: 5.3–13.3), although not significantly, than that for LCIS (4.2, 95% CI: 1.1–10.7).

Seven cases of cancer other than breast or non-melanomatous skin cancer were observed *vs.* 6.9 expected (SIR = 1.0, 95% CI: 0.4–2.1). These included 1 neoplasm of the oropharynx (SIR = 17.2), 1 of the colon/rectum (SIR = 0.8), 1 of the gallbladder (SIR = 5.8), 2 of the lung (SIR = 4.0), 1 melanoma of the skin (SIR = 2.7) and 1 of the ovary (SIR = 2.1). In addition, 6 cases of non-melanomatous skin cancer were observed *vs.* 3.3 expected (SIR = 1.9). None of these estimates was significant. If all cancers, including breast cancer, were considered together, the excess would have been of 2.7-fold (95% CI: 1.9–3.8).

Corresponding figures for DCIS in strata of years since diagnosis and age are given in Table III. No pattern of risk with time since diagnosis was evident, with SIR of breast cancer of 8.0 in the first year, 6.5 between 1 and 4 years and 11.7 after ≥5 years. The SIR of breast cancer after DCIS was 11.0 in women below age 55 years and 7.1 in those aged 55 years or over. No meaningful pattern was observed for other neoplasms or, due to the limited number of cases diagnosed, for breast cancer after LCIS.

The cumulative risk of invasive breast cancer (including ipsilateral and contralateral breast cancer) at various time intervals following diagnosis of CIS is shown in Figure 1. The estimated cumulative risk was 7% after 5, 16% after 10 and 24% after 15 years.

A comparison of the breast side and the histological type of CIS with that of subsequent invasive cancer of the breast was possible for 23 women (*i.e.,* all except 1 in whom invasive cancer emerged as metastatic disease). In 13/19 DCIS, invasive cancer occurred in the same breast, compared to 2/4 LCIS. Furthermore, in 16 of 19 DCIS, subsequent invasive breast cancer was ductal, while in 3 of 4 LCIS it was lobular. Three DCIS were followed by not otherwise specified carcinomas of the breast, and one LCIS was followed by a ductal carcinoma of the other breast.

Finally, 6 deaths from cancer of the breast were found *vs.* 1.5 expected. The standardized mortality ratio was 4.0 (95% CI: 1.5–8.7), whereas the cumulative risk of death was 4% at 10 and 10% at 15 years.

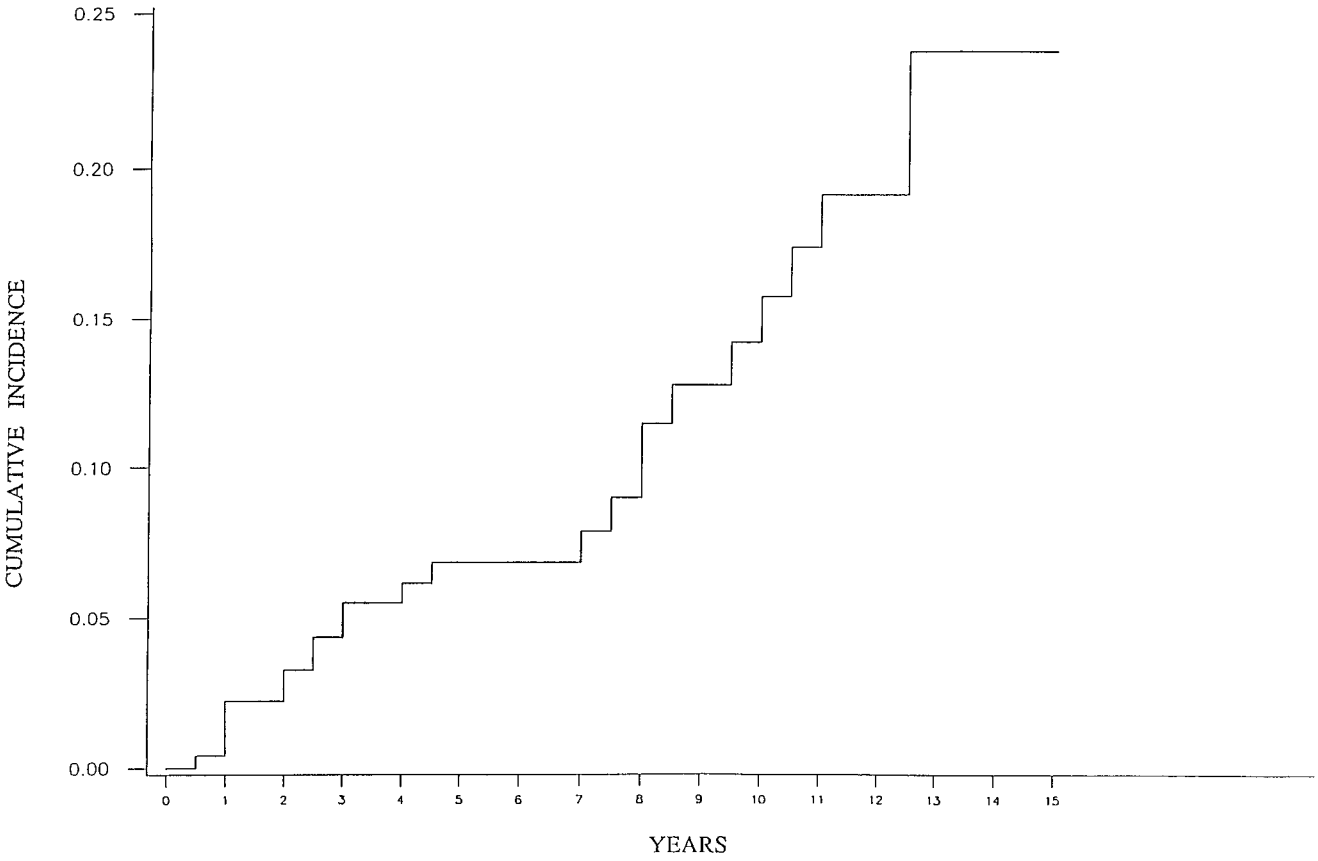

FIGURE 1 – Cumulative incidence of invasive breast cancer (n = 24) following 249 CIS of the breast: Vaud, Switzerland, 1977–1994.

DISCUSSION

Our results show that, after an initial diagnosis of CIS of the breast, women were at about 7-fold increased risk of developing an invasive second breast cancer. Such increase was of similar magnitude in different strata of age and years since CIS diagnosis. Most data refer to DCIS, but the pattern of risk was similar for LCIS. A 4-fold excess was found for breast cancer mortality.

A limitation of the present study, which is based on cancer registration data, is the lack of detailed information on selected clinicopathological characteristics, such as site and margin status, which may have relevant prognostic implications (Cheng *et al.,* 1997). With respect to treatment, a review of pathological reports available at Vaud Cancer Registry suggested that mastectomy was performed in 34% of DCIS and 25% of LCIS, indicating that mastectomy is comparatively low in this population (Ernster *et al.,* 1996; Habel *et al.,* 1997).

Among the strengths of our study, there are its population basis, which should render any inference relatively free from selection bias (Levi *et al.,* 1996), and the complete histological verification of CIS cases. The absence of excess risk for any of the other cancer sites is also reassuring with respect to surveillance bias.

Still, diagnosis of CIS of the breast may be more frequent in women at higher baseline risk of breast cancer. Furthermore, the issue of exclusion of synchronous neoplasms remains open to discussion, since the extensive examination of the breast performed at the time of original diagnosis of CIS may produce a reduction of subsequent breast cancer risk in these women. These same women, however, are likely to be subject to increased surveillance of their breasts, and this could increase the likelihood of a breast neoplasm being diagnosed. The persistence of risk many years after initial CIS diagnosis and the absence of any excess for secondary cancer other than breast weigh, in any case, against the possibility of the breast cancer excess being due to ascertainment bias.

In our study, the risk of developing breast cancer was similar to that reported in clinical series of women who did not undergo mastectomy (Betsill *et al.,* 1978; Fisher *et al.,* 1993; Page *et al.,* 1982), although higher than in those in whom the entire breast was removed (Schnitt *et al.,* 1988). In a group of 28 women with DCIS (Page *et al.,* 1982), 7 evolved as invasive breast cancer within 10 years, and 9 after 30 years, with a risk about 9-fold higher than the general population. In a randomized comparison of 391 women treated with lumpectomy and 399 treated with lumpectomy followed by radiation therapy, cumulative 5-year incidence was approximately 12% and 5%, respectively (Fisher *et al.,* 1993). Such risk is close to (Broet *et al.,* 1995), if not higher than (Levi *et al.,* 1993), the risk of contralateral second cancer in women with invasive breast cancer. In a population-based study from western Washington (Habel *et al.,* 1997), the rate of contralateral invasive breast cancer was approximately twice the population rate for DCIS and 3 times the population rate for LCIS. The cumulative incidence of breast cancer at 10 years was about 6% for DCIS and 8% for LCIS. These estimates are lower than ours, but the comparison is hampered by the difference in endpoint (contralateral *vs.* all breast cancer), degree of surveillance and type of treatment. Largely due to high rates of prophylactic mastectomy, in fact, Habel *et al.* (1997) showed extremely elevated rates of second DCIS in the first follow-up year.

Albeit numbers were limited, our data provide some hints also on the difference between DCIS and LCIS and the laterality issue (Page and Jensen, 1996). Little affected by mammographic screening, LCIS have been excluded in most recent analyses on CIS (Schnitt *et al.,* 1988; Ernster *et al.,* 1996; Morrow, 1996). Haa-

gensen *et al.* (1978) followed, for an average of 13 years, 209 women with LCIS. Thirty-five breast carcinomas emerged, compared to 5 expected. Cumulative risk was about 7% at 10 years. In our study, LCIS represented 24% of CIS, occurred at a younger age and showed an association with subsequent invasive cancer which appeared somewhat lower than that of DCIS. In agreement with previous data (Fisher *et al.,* 1993; Webber *et al.,* 1981), however, DCIS, but not LCIS, tended to be followed more often by ipsilateral than by contralateral breast cancer.

The close correlation between the presence of ductal or lobular features in the initial CIS and in the subsequent invasive cancer is in agreement with the findings of Habel *et al.* (1997) and supports the specificity of the 2 lesions. As shown in a review of nearly 120,000 breast cancers from the Surveillance Epidemiology and End Results Program of the United States (Stalsberg and Thomas, 1993), lobular carcinoma arises from the most steroid hormone-dependent part of the breast and shows a more marked premenopausal hook than ductal carcinoma. Conversely, about 50% of DCIS may be estrogen receptor negative (Holland *et al.,* 1997).

The lack of more detailed information on CIS characteristics and treatment is of major concern. This caution notwithstanding, if, with the present approach, 15–25% of CIS recur as invasive disease and 4–10% may die of breast cancer within 10–15 years, adequate surveillance and clinical management of these lesions are clearly needed.

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