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Survival of young and older breast cancer patients in Geneva from 1990 to 2001

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Abstract

The effect of age on breast cancer survival is still a matter of controversy. Breast cancer in young women is thought to be more aggressive and to have worse prognosis but results from clinical research have been neither consistent nor definitive. In this study, we have assessed the impact of young age at diagnosis on tumor characteristics, treatment and survival of breast cancer. The study included 82 very young (⩽35 years), 790 young (36–49), and 2125 older (50–69) women recorded between 1990 and 2001 at the Geneva Cancer Registry. Very young and young patients had more often stage II cancers ($P = 0.009$), poorly differentiated ($P < 0.001$) and estrogen receptor negative ($P < 0.001$) tumors. They were also more likely to receive chemotherapy ($P < 0.001$) and less likely to receive hormonal therapy ($P < 0.001$). Specific five-year survival was not different in the three groups (91%, 90%, and 89% for very young, young and older, respectively). When adjusting for all prognostic variables, age was not significantly related to mortality from breast cancer with a hazard ratio of 0.8 (95% CI: 0.3–2.0) for very young and 1.1 (95% CI: 0.8–1.4) for young patients compared to older women. Tumor stage, differentiation, estrogen receptor status, surgery, and radiotherapy were all independent determinants of breast cancer prognosis. We conclude that age is not an independent prognostic factor when accounting for breast tumor characteristics and treatment.

Keywords: Breast cancer; Young; Prognosis; Survival

1. Introduction

Breast cancer before the age of 50 is relatively uncommon, nevertheless, 15–25% of all women diagnosed with breast cancer are in their thirties or forties. Furthermore, in Western countries breast cancer is the main cause of death among women aged 15–49 years [1,2]. Many authors have suggested that breast cancer in young women is biologically different from that of older women. Specifically, the tumors progress faster, present with higher grade and are more often estrogen receptor negative than tumors in older patients [3–7]. Diagnosis is often delayed in young women and cancers are larger and more advanced and less often screen-detected [6,7]. The prognosis and survival of young women with breast cancer remains a controversial issue as several studies have shown discordant results. Many studies have

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shown that survival among young women is worse than that of older women [6,8–12]. Other studies have found that age is not related to disease-free or overall survival after adjustment for other prognostic variables [13–17]. Some have even reported that young patients have better survival [18–20]. Only a limited number of these studies, however, were population-based [6,11,12,16–20].

In this work, we have aimed to assess the impact of young age at diagnosis on clinical presentation, pathological features and prognosis of breast cancer among women from the canton of Geneva, Switzerland.

2. Patients and methods

Data collected by population-based Geneva Cancer Registry was used in this work. The registry records information on all incident cases of cancer occurring in the canton (approximately 420 000 inhabitants). Registration is based on several sources of information and individual clinical files from all public university hospitals are systematically consulted and inquiry forms are regularly sent to physicians for patients treated in the private sector. Less than 2% of cases are recorded from death certificates only [21]. Recorded data include socio-demographic characteristics, diagnostic circumstances, modalities of diagnostic assessment, tumor characteristics coded according to the International Classification of Diseases for Oncology (ICD-O) [22], stage of disease at diagnosis, treatment during the first six months after diagnosis, survival and cause of death. In addition to passive follow-up (routine examination of death certificates and hospital records), the registry regularly assesses survival through an active follow-up performed routinely each year using the files of the Cantonal Population Office, which is in charge of the registration of the resident population. For all dead patients, the registry medical staff systematically consults medical files or/and write to practitioner to assess cause of death and codes the cause according to the WHO classification [23].

In this study, we have included all women with histologically confirmed primary carcinoma of the breast (ICD-O code: 174) aged <70 years, diagnosed between 1990 and 2001, and resident in the Swiss canton of Geneva. Since detailed information on type of surgery was available only from the end of the 1980s, we did not include patients recorded before 1990. We excluded women who were diagnosed on the day of their death ($n = 2$) and those for which no information at the follow-up was available ($n = 3$). The final study included 2997 patients. There were 72 cases (2.4%) of synchronous breast cancers. For these patients only one cancer was considered in the analysis. If the stages between the two cancers differed, the one with the more advanced stage was considered in the analysis.

Stage at diagnosis was based on the tumor, node and metastasis TNM classification system [24]. We considered the pathological pTNM or, when absent, the clinical cTNM classification. Tumor was classified as Tis (*in situ*), T0 (non-palpable), T1 ($\leqslant$2 cm), T2 (>2–5 cm), T3 (>5 cm), T4 (extension to chest wall/skin and inflammatory carcinoma) and TX (unknown, not pertinent). Lymph node invasion was classified as N0 (no invasion), N1 (movable axillary), N2 (fixed axillary), N3 (infraclavicular, internal mammary, or supraclavicular) and NX (unknown) and metastasis as M0 (absent), M1 (present) or MX (unknown). Stages were classified into seven groups: *in situ* (Is), stage I, stage IIA (T0 or T1 and N1, T2 N0), stage IIB (T2 N1, T3 N0), stage lll, stage lV, and unknown. Histology was grouped into three categories: ductal, lobular, other. The histological grading was grouped into four categories: well differentiated, moderately differentiated, poorly differentiated/undifferentiated, unknown (not stated or not applicable). Estrogen receptor status, routinely recorded only since 1995, was considered as positive ($\geqslant$10%), negative (<10%), or unknown. Socio-economic status was based on the woman's last occupation or, for the unemployed, that of the spouse. Four levels were considered as follows: low (manual employees, skilled and unskilled workers), middle (non-manual employees and administrative staff), high (professionals, executives, administrators), and unknown [25]. The methods of discovery were regrouped into four categories: mammography screening, breast self-examination, symptoms and other circumstances (including unknown). The treatments examined were surgery (mastectomy, breast conserving surgery, no surgery), radiotherapy (yes, no), chemotherapy (yes, no) and hormonal therapy (yes, no).

Survival since the date of diagnosis of first cancer was considered. The incidence index date refers to the date of confirmation of diagnosis or to the date of hospitalisation if it precedes the diagnosis and is related to the disease. Death from breast cancer was the considered event and subjects alive at the end of follow-up (December 31, 2002), lost to follow up or deceased from other causes were censored at the date of their last observation.

Patient characteristics, clinical presentation, tumour characteristics, treatment and outcome were compared between three age groups: $\leqslant$35, 36–49, and 50–69 years old, using Pearson's χ^2 test. All reported P values were two-sided. The five-year breast cancer-specific survival rates were estimated according to age group by the actuarial method (intervals in years and standard error according to Greenwood [26]). To evaluate the independent effect of age at diagnosis on survival from breast cancer, we performed a multivariate Cox regression model that included all variables with a significant effect in the univariate analysis. Women aged 50–69 years, representing the largest group, were chosen as reference.

To investigate if the effect of age was similar within different therapeutic groups, we performed interaction tests by introducing in the Cox model interaction terms involving age and treatment [27]. We also performed subgroup analyses to separately evaluate the effect of age among women who did and who did not receive chemotherapy.

3. Results

Among the 2997 women with breast cancer included in this study, 82 (3%) were diagnosed at ⩽35 years of age, 790 (26%) between 36 and 49 years of age, and 2125 (71%) between 50 and 69 years of age. Table 1 shows patient and tumour characteristics, the circumstances of diagnosis, and the treatments by age at diagnosis. Socio-economic status was higher among women aged 36–49 years than among the younger or the older women ($P < 0.001$). The proportion of cancers discovered through breast self-examination decreased with age from 44% to 35% to 22% among women ⩽35 years, 36–49 years and women 50–69 years old, respectively ($P < 0.001$). Very young (⩽35 years) and young (36–49 years) patients were less likely to be diagnosed with a cancer *in situ* or stage I, but more often with a stage IIA and stage IIB tumour ($P = 0.009$). Cancer in patients aged <50 years presented poorer tumoural prognosis. Poorly differentiated tumours accounted for 37%, 29% and 22% of the tumours among women aged ⩽35, 36–49, and 50–69 years old, respectively ($P < 0.001$) and tumours negative for estrogen receptors were the 23%, 15% and 9%, respectively ($P < 0.001$). The three age groups did not show any difference by histological type. The proportion of mastectomy or breast conserving surgery was equally distributed among the three age groups as was the proportion of patients treated with radiotherapy after breast conserving surgery. Conversely, women aged <50 years were more likely to receive chemotherapy (68% in the group ⩽35 years, 61% in those 36–49 years and 38% in those 50–69 years old, $P < 0.001$), and less likely to receive hormonal therapy (31% in the group ⩽35 years, 38% in the 36–49 years and 59% in the 50–69 years old, $P < 0.001$).

At the end of follow-up 2512 (84%) women were still alive, 162 (5%) had moved from the Canton (lost to follow-up), and 323 (11%) had deceased. The women were followed-up for a median of 56 months. The five-year specific breast cancer survival rate was 91% (95% CI: 83–99%) in women aged ⩽35 years old, 90% (95% CI: 87–92%) in women 36–49 years old and 89% (95% CI: 88–91%) in women 50–69 years old (Fig. 1).

Table 2 presents the risk [Hazard Ratio (HR)] of dying of breast cancer according to age, patient and tumour characteristics, and treatments. In crude analyses, the risk of breast cancer death was 1.0 (95% CI: 0.7–1.3) in women 36–49 years old and 0.7 (95% CI: 0.3–1.8) in women aged ⩽35 years compared to women 50–69 years old. Socio-economic status, method of discovery, stage, histology, differentiation, estrogen receptor status, surgery, radiotherapy, hormonal therapy and chemotherapy were all related to the risk of dying of breast cancer. In the multivariate analysis, we included all the variables with significant effect on prognosis. After adjustment, age was still not a significant prognostic factor for breast cancer mortality with HR = 1.1 (95% CI: 0.8–1.4), HR = 0.8 (95% CI: 0.3–2.0) for women 36–49 years old and ⩽35 years old, respectively, compared to 50–69 years old. In multivariate analysis, the woman's socio-economic status, tumour stage at diagnosis, tumour differentiation, estrogen receptor status, radiotherapy and type of surgery were independently and significantly linked to breast cancer mortality. The interaction tests performed between age and treatments were not statistically significant. In the stratified analysis by use of chemotherapy, the effect of age was not statistically different between women who received and who did not receive chemotherapy.

4. Discussion

This study shows that young women with breast cancer present with more advanced and aggressive tumours and receive chemotherapy more often than other patients. However, disease specific survival of young women did not differ from that of older patients. After taking into account differences in prognosis and treatment between age groups, the risk of dying of breast cancer was similar among very young (⩽35 years), young (36–49 years) and older women (50–69 years).

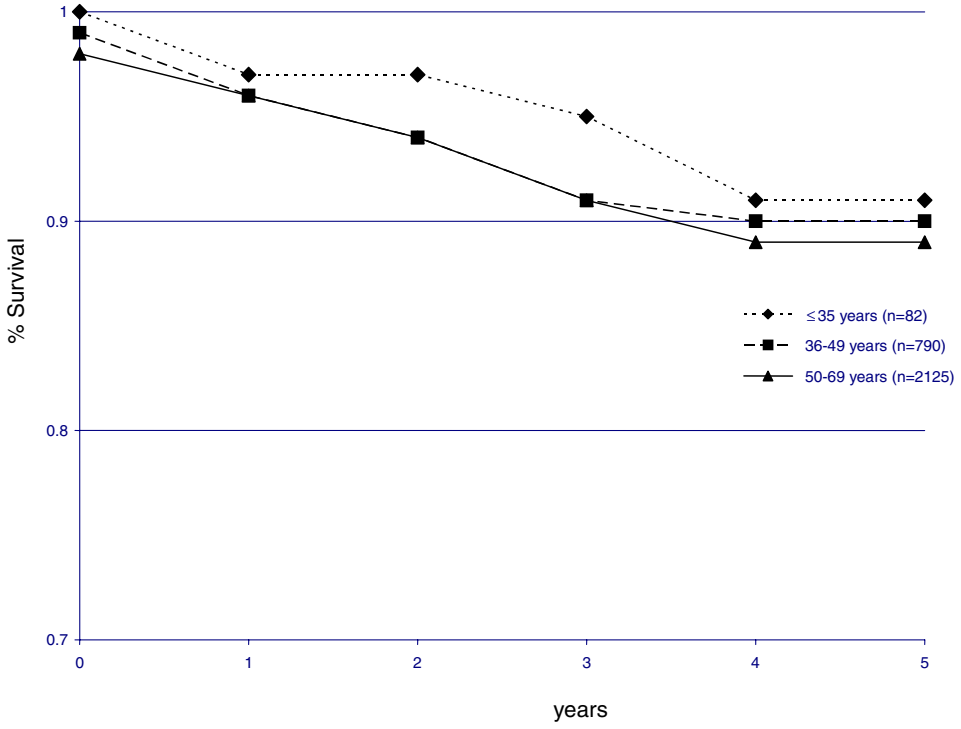
Data of our study are derived from a population-based cancer registry with information on the most important prognostic variables such as tumour size, stage, differentiation and unlike other studies we could also adjust for treatment, including the use of chemotherapy. We could not evaluate the risk of recurrence according to age, because the Geneva Registry does not routinely collect this information. Also, the relatively small size of the study population, particularly for the group aged ⩽35 years, limited the statistical power of separate subgroup analyses. For this reason, we could not correctly evaluate the effect of age according to therapeutic groups and tumour characteristics, such as estrogen receptor status. The study of the differences in breast cancer-specific survival by age can be biased due to lower accuracy of the cause of death in death certificate among older women. We believe this bias is minimal in this study because women older than 70 years were not considered and because cause of death was searched systematically in the medical files.

Table 1
Patient and tumor characteristics, circumstances of diagnosis and treatment by age at diagnosis in 2997 breast cancer patients

	Age in years						*P* value for heterogeneity
	⩽35		36–49		50–69		
	N = 82	%	*N* = 790	%	*N* = 2125	%	
Socio-economic status							<0.001
Low	15	18.3	128	16.2	343	16.1	
Middle	33	40.2	259	32.8	658	31.0	
High	4	4.9	151	19.1	304	14.3	
Unknown	30	36.6	252	31.9	820	38.6	
Method of discovery							<0.001
Mammography screening	0	–	59	7.5	519	24.4	
Self-examination	36	43.9	274	34.7	475	22.4	
Symptoms	28	34.1	254	32.2	559	26.3	
Other circumstances	18	22.0	203	25.7	572	26.9	
Stage							0.009
Is	6	7.3	67	8.5	185	8.7	
I	29	35.4	246	31.1	848	39.9	
IIA	23	28.0	234	29.6	511	24.0	
IIB	16	19.5	143	18.1	325	15.3	
III	5	6.1	50	6.3	138	6.5	
IV	1	1.2	23	2.9	69	3.2	
Unknown	2	2.4	27	3.4	49	2.3	
Histology							0.085
Ductal	73	89.0	649	82.2	105	80.2	
Lobular	2	2.4	80	10.1	251	11.8	
Other	7	8.5	61	7.7	169	8.0	
Differentiation							<0.001
Well	11	13.4	178	22.5	581	27.3	
Moderate	30	36.6	277	35.1	775	36.5	
Poor	30	36.6	226	28.6	468	22.0	
Unknown	11	13.4	109	13.8	301	14.2	
Estrogen receptor status							<0.001
Negative	19	23.2	117	14.8	202	9.5	
Positive	30	36.6	321	40.6	1088	51.2	
Unknown	33	40.2	352	44.6	835	39.3	
Surgery							0.188
Mastectomy	32	39.0	275	34.8	674	31.7	
Breast conserving surgery	49	59.8	483	61.1	1348	63.4	
No surgery	1	1.2	32	4.1	103	4.8	
Radiotherapy							0.593
Yes	61	74.4	557	70.5	1533	72.1	
No	21	25.6	233	29.5	592	27.9	
Chemotherapy							<0.001
Yes	56	68.3	478	60.5	810	38.1	
No	26	31.7	312	39.5	1315	61.9	
Hormonal therapy							<0.001
Yes	25	30.5	297	37.6	1253	59.0	
No	57	69.5	493	62.4	872	41.0	

Geneva 1990–2001.

In accordance with our results, other studies have also reported more advanced and aggressive tumours among young women [6,15]. Delayed diagnosis is probably partly due to the fact that the breast tissue of younger women is denser and therefore more difficult to examine clinically and by mammography. Apart from a familial risk context, young women are in general not covered by mammography screening. Because of the lower probability of having breast cancer at young age, both women and physicians might perform self-examination or clinical examination less often and minimise putative abnormalities [28]. A more advanced stage at diagnosis may also reflect a rapidly growing tumour. Special endocrine and immunological factors and/or genetic differences more frequent in younger women who develop breast cancer maybe linked to tumour invasiveness [29].



Number of patients at risk at beginning of each period

Age	Years					
	0	1	2	3	4	5
50-69	2125	2057	1729	1439	1184	949
36-49	790	764	655	557	483	417
≤ 35	82	79	66	53	46	39

* Only deaths from breast cancer are considered. Survival curves are derived from actuarial method;

P value of log-rank test =0.2863.

Fig. 1. Five-year breast cancer-specific survival by age *. Geneva 1990–2001.

Our findings contrast with studies showing a worse survival among young patients [6,8–12,30]. However, in some of these studies the observations are drawn from a single centre and selection may have taken place during the process of referring patients to the centre [8–10]. In other studies, the cumulative survival rates are crude or mortality risks are not adequately adjusted for other important prognostic factors, including stage of the disease and treatment, particularly chemotherapy [6,12,31]. Our findings are consistent with other population-based studies showing no difference in survival by age at diagnosis [16,17].

Current guidelines consider breast cancer patients age <35 years at high risk of relapse and/or mortality and recommend adjuvant chemotherapy irrespective of the stage of their tumour [32]. Furthermore, Kroman and colleagues have clearly demonstrated the unfavourable effect of young age in patients having no adjuvant therapy [17]. In Geneva almost 70% of the women aged ⩽35 years received adjuvant chemotherapy. This high rate of systemic chemotherapy provided to young patients, the possible endocrine effects of chemotherapy in these women, together with a relatively early diagnosis of cancer made at young age (almost 90% of breast cancers among women age ⩽35 years were stage I or II) may account for the failure to see a prognostic effect of age. We conclude that when standard care is offered to young women, their prognosis is not worse than that of their older counterpart.

Conflict of interest statement

None declared.

Table 2
Relative risk [Hazard Ratios (HR)] of dying after diagnosis of breast cancer according to age at diagnosis, tumor characteristics, method of discovery and treatment in 2997 breast cancer patients

	Crude HR	95% CI	Adjusted HR[a]	95% CI
Age (years)				
50–69	1.0	–	1.0	–
36–49	1.0	0.7–1.3	1.1	0.8–1.4
⩽35	0.7	0.3–1.8	0.8	0.3–2.0
Method of discovery				
Mammography screening	1.0	–	1.0	–
Self-examination	2.3**	1.3–4.2	0.7	0.4–1.4
Symptoms	5.4***	3.1–9.3	1.2	0.7–2.3
Other circumstances	2.1*	1.2–3.8	0.9	0.5–1.6
Socio-economic status				
Low	1.0	–	1.0	–
Middle	0.7*	0.5–1.0	0.9	0.7–1.3
High	0.4***	0.3–0.6	0.5	0.3–0.9
Unknown	0.6**	0.4–0.8	0.6	0.4–1.0
Stage				
Is	1.0	–	1.0	–
I	1.0	0.4–2.6	1.6	0.6–4.4
IIA	2.7*	1.1–6.8	3.5*	1.3–9.3
IIB	6.6***	2.7–16	7.0***	2.6–19
III	12***	4.6–29	11***	4.0–30
IV	54***	22–135	24***	8.4–68
Unknown	7.3***	2.5–21	6.1**	2.0–19
Histology				
Ductal	1.0	–	1.0	–
Lobular	1.2	0.8–1.8	1.3	0.8–2.1
Other	4.3***	3.2–5.8	0.9	0.6–1.4
Differentiation				
Well	1.0	–	1.0	–
Moderate	4.8***	2.5–9.4	2.9**	1.4–5.9
Poor	11***	5.7–21	5.2***	2.6–10
Unknown	12***	6.1–23	3.1**	1.5–6.7
Estrogen receptor status				
Negative	1.0	–	1.0	–
Positive	0.2***	0.2–0.3	0.3***	0.2–0.5
Unknown	0.6**	0.4–0.8	0.5***	0.3–0.7
Surgery				
Mastectomy	1.0	–	1.0	–
Breast conserving surgery	0.3***	0.2–0.4	0.7*	0.5–1.0
No surgery	5.7***	4.2–7.8	2.6**	1.6–4.2
Radiotherapy				
Yes	1.0	–	1.0	–
No	3.1***	2.4–4.0	1.7**	1.2–2.3
Chemotherapy				
Yes	1.0	–	1.0	–
No	0.4***	0.3–0.6	1.2	0.8–1.6
Hormonal therapy				
Yes	1.0	–	1.0	–
No	1.5**	1.2–2.0	1.2	0.9–1.6

Geneva 1990–2001.

[a] Adjusted for age, method of discovery, socioeconomic status, stage, histology, differentiation, estrogen receptor status, surgery, radiotherapy, chemotherapy, and hormonal therapy.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

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