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Abstract To explore the effect of age at diagnosis on relative survival from breast cancer at different cancer stages and grades, using appropriate statistical modeling of time-varying and non-linear effects of that prognostic covariate. Data on 4,791 female invasive breast cancers diagnosed between 1990 and 1997 were obtained from a French cancer registry. The effect of age on relative survival was studied using an approach based on excess rate modeling. Different models testing non-linear and non-proportional effects of age were explored for each grade and each stage. In the whole population, the effect of age was not linear and varied with the time elapsed since diagnosis. When analyzing the different sub-groups according to grade and stage, age did not have a significant effect on relative survival in grade 1 or stage 3 tumors. In grade 2 and stage 4 tumors, the excess mortality rate increased with age, in a linear way. In grade 3 tumors, age was a time-dependent factor: older women had higher excess rates than younger ones during the first year after diagnosis whereas the inverse phenomenon was observed 5 years after diagnosis. Our findings suggest that when taking into account grade and stage, the time-varying impact of young age at diagnosis is limited to grade 3 tumors, without evidence of worst prognosis at 5 years for the youngest women.

Keywords Breast neoplasm · Registry · Survival analysis · Proportional hazard models · Age · Relative survival

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Introduction

Breast cancer is the most common cancer and a leading cause of death among women worldwide. Survival studies appear thus as essential for evaluating the availability and effectiveness of relevant therapies. Among other indicators of survival, a number of studies considered the concept of net survival: i.e., the risk of dying from breast cancer when other causes of death are ruled out. Comparing the two ways to calculate net survival, relative survival, contrarily to disease-specific survival, is able to estimate net survival without the need for information on the cause of death.

In breast cancer, several studies suggested that young women up to 40 years old have poorer relative survivals than middle-aged women [1–5]. Moreover, international expert consensuses [6, 7] have considered age under 35 as a discriminatory feature of increased risk and have used age to determine treatment strategies. Several authors have explained the poorer outcome in young women by more aggressive tumor characteristics. Indeed, poorly differentiated [2, 5, 8–11] and lymph-node-positive [2, 8, 10, 12, 13] tumors were more frequently observed in young

than in old women. Increased tumor sizes have been also implicated [8, 9].

Besides, some authors have reported that age would loose its significant prognostic impact on relative survival after adjustment for tumor characteristics [14, 15] whereas others have found that age would remain an independent prognostic factor even after such an adjustment [2, 4]. Disease-specific survival analyses yielded also conflicting results. According to Maggard et al. [9] age at diagnosis remained a significant factor after controlling for other prognostic factors while Rapiti et al. did not find an independent effect of age on survival [11]. Thus, the relationship between age and net survival in breast cancer is still debated.

In most above-cited studies, age was introduced as a categorical variable and the assumption of a constant effect of age over time (proportional assumption) have been seldom checked though the results could be misleading if that assumption is not met. The results of a French population-based relative survival study [16] have shown that the effect of age at diagnosis on the excess mortality rate was not log-linear and varied with the time elapsed since diagnosis. In that study, no prognostic factors other than age and year of diagnosis could be taken into account because cancer registries did not routinely collect clinical data. Besides, only two disease-specific survival analyses [17, 18] have introduced age as a continuous variable and tested the non-proportional and non-linear effects of age taking into account other prognostic factors. They have found a non-linear and/or a time-dependent effect of age at diagnosis when cancer grade, tumor size, cancer stage, and node metastasis were taken into account. According to Tai et al. [18], young women had a higher mortality rate than older ones, and the risk of death from breast cancer decreased with longer follow-up. Rosenberg et al. [17] have shown that the effect of age varied over time and that "younger age groups matched or even fell bellow the survival rate of the oldest group over time".

The aim of the present study was to model the effect of age at diagnosis (as continuous variable) on the relative survival taking into account cancer stage and grade and using a non-linear and non-proportional model.

Materials and methods

Data source

The data were collected by the population-based Cancer Registry of Isère, France. In 1990, the year systematic breast cancer screening program was initiated in that Département, its cancer registry was covering a population of nearly one million inhabitants.

The present study included all women aged ≥15 years with a primary invasive breast cancer, diagnosed between January 1, 1990 and December 31, 1997. Sarcomas, lymphomas, and Paget's diseases were excluded. Overall, 4,791 women were included.

Variables of interest

In the present article, those variables were age at diagnosis, tumor stage, and Scarff-Bloom-Richardson (SBR) histological grade. Patients were staged according to the American Joint Committee on Cancer system and on basis of pTNM, the post surgical histopathological classification.

Nearly half the information about metastasis was missing. After checking the procedures of data collection of the cancer registry, a lack of information was considered as "no metastasis", especially that the proportion of patients with metastasis was in agreement with the proportions found by other French population-based studies [1, 15].

The SBR grade was available for nearly 75% of women and the cancer stage for more than 80%. Cases with missing information about grade or stage were studied as a separate category. Actually, four grades (one to three plus an "unknown grade") and five stages (one to four plus an "unknown stage") were defined.

Statistical analysis

Descriptive statistics

The relationship between grade, stage, and age was explored with a test of independence.

Univariate analysis

The duration of follow-up was defined as the time elapsed from the date of diagnosis to the date of death or, in case no death occurred, to the date of the last observation. An active search for the vital status on the 1st of January 2002 was carried out using a standardized administrative procedure. Alive patients were censored on the 1st of January 2002. Relative survival was estimated using an excess rate model [19]. In each subject, the observed mortality rate at time t was considered to have two components: one due to cancer (λc) and another due to other causes. The former component may be viewed as the excess mortality rate due to cancer and the latter as the mortality rate from causes other than cancer; i.e., the expected mortality rate. The expected mortality rates through the period 1989–2001 in all French Departments were obtained from the Institut National de la Statistique et des Etudes Economiques (INSEE).

The excess rate was modeled using a smoothed parametric function of time chosen among several

candidates. The selection of the best model was based on the Akaike Information Criterion (AIC). That method allowed to describe the evolution of the excess mortality with time elapsed since diagnosis. We could then calculate the survival probabilities at different times (by means of exponentiation of the corresponding cumulative excess rates) in the different subgroups defined by age class, grade, and stage. The detailed method is described elsewhere [19].

Modeling the effect of age at diagnosis

The effect of age at diagnosis was studied during the first five years of the follow-up. To take into account cancer grade, we performed the statistical analysis of the age effects with each cancer grade separately rather than using a hypothetical and complex model with age and grade as covariables. For each grade, the excess mortality rate was modeled as a parametric function of the time elapsed since diagnosis and of age at diagnosis. Age at diagnosis was considered as a continuous variable. The non-linearity effect of age was modeled by a cubic regression spline with a knot at the mean age at diagnosis. The non-proportional effect of age reflected the fact that the effect of age changes with the time elapsed since diagnosis; it was explored by introducing into the model an interaction term between age and the time elapsed since diagnosis. The interaction term and the baseline hazard were cubic splines with knots at one year follow-up. In order to test the non-proportional and non-linear effects of age, models were selected among

Table 1 Characteristics of the 4,791 women with primary invasive breast cancer aged ≥15 years, diagnosed between January 1, 1990 and December 31, 1997—Cancer Registry of Isère, France

	<35 years	35–49 years	50–64 years	65–74 years	≥75 years	Total
Cancer grade						
1	4 (4)[a]	224 (18)	393 (24)	221 (22)	137 (17)	979 (20)
2	27 (28)	411 (34)	541 (33)	360 (36)	252 (31)	1591 (33)
3	38 (40)	304 (25)	359 (22)	177 (18)	133 (16)	1011 (21)
Unknown	26 (27)	284 (23)	361 (22)	247 (25)	292 (36)	1210 (25)
Total	95 (100)	1223 (100)	1654 (100)	1005 (100)	814 (100)	4791 (100)
Cancer stage						
1	27 (28)	496 (41)	753 (46)	429 (43)	137 (17)	1842 (38)
2	41 (43)	450 (37)	614 (37)	345 (34)	229 (28)	1679 (35)
3	3 (3)	38 (3)	72 (4)	48 (5)	53 (7)	214 (4)
4	3 (3)	34 (3)	81 (5)	64 (6)	61 (7)	243 (5)
Unknown	21 (22)	205 (17)	134 (8)	119 (12)	334 (41)	813 (17)
Total	95 (100)	1223 (100)	1654 (100)	1005 (100)	814 (100)	4791 (100)
Tumor size (pT)						
0	0 (0)	1 (0)	2 (0)	0 (0)	1 (0)	4 (0)
1	45 (47)	738 (60)	1060 (64)	572 (57)	269 (33)	2684 (56)
2	27 (28)	242 (20)	362 (22)	247 (25)	203 (25)	1081 (23)
3	5 (5)	23 (2)	41 (2)	25 (2)	21 (3)	115 (2)
4	2 (2)	25 (2)	59 (4)	37 (4)	81 (10)	204 (4)
Unknown	16 (17)	194 (16)	130 (8)	124 (12)	239 (29)	703 (15)
Total	95 (100)	1223 (100)	1654 (100)	1005 (100)	814 (100)	4791 (100)
Lymph nodes (pN)						
N−	40 (42)	678 (55)	938 (57)	579 (58)	277 (34)	2512 (52)
N+	46 (48)	458 (37)	611 (37)	325 (32)	225 (28)	1665 (35)
Unknown	9 (9)	87 (7)	105 (6)	101 (10)	312 (38)	614 (13)
Total	95 (100)	1223 (100)	1654 (100)	1005 (100)	814 (100)	4791 (100)
Metastases						
0	53 (56)	459 (38)	673 (41)	382 (38)	228 (28)	1795 (37)
1	3 (3)	34 (3)	81 (5)	64 (6)	61 (7)	243 (5)
Unknown	39 (41)	730 (60)	900 (54)	559 (56)	525 (64)	2752 (57)
Total	95 (100)	1223 (100)	1654 (100)	1005 (100)	814 (100)	4791 (100)

[a] Number (percentage)

five functions using the AIC criterion (Cf. Appendix Table 4).

Cancer stage was taken into account following the same strategy as above. Recently, Abrahamowicz et al. have shown that the non-linear and time-dependent effects of age should not be tested independently [20]. For that reason, time-dependent and non-linear effects were tested simultaneously.

The analyses were carried out using homemade programs run on S-plus software (version 6).

Results

Descriptive statistics

The median age at diagnosis of the 4,791 patients was 60 years (range 23–100 years). In those who were still alive at end of follow-up, the median follow-up was 7 years.

Table 1 shows the characteristics of those patients by age classes. Women <35 had significantly higher grades and more frequently positive nodes than women aged ≥35 ($P < 0.05$ in both tests).

Unvariate analysis

The relative survival of the whole population at 1, 3, and 5 years was 97, 92, and 87%, respectively. The lowest 5-year relative survival was observed in the youngest age group (<35) whereas, at one year follow-up, the lowest survival was observed in women aged ≥75 (Table 2). Women aged 35–49 had the best prognosis of all age groups. The relative survival rate decreased with the increase in grade and in stage (Table 2).

Modeling the effect of age at diagnosis

The model selected for the whole population was the non-linear and non-proportional model: the effect of age at diagnosis was not linear and varied with the time elapsed since diagnosis. Three months after diagnosis, the hazard ratio increased with age whereas five years after diagnosis young women were at higher risks of death than middle-aged or elderly women (Fig. 1 and Appendix Table 5).

Table 3, Fig. 2 and Appendix Table 5 show the effect of age at diagnosis according to different grades and stages.

Age did not have a significant effect on relative survival in women with grade 1 or stage 3 tumors; nevertheless, with grade 1, the functions with non-proportional or non-linear effect of age did not converge because of a low mortality rate in that group.

Table 2 Relative survival by age group, grade, and stage [95% confidence intervals]

	1 year survival	3 years survival	5 years survival
All women	97 [97; 98]	92 [91; 92]	87 [86; 88]
Age group			
<35	95 [93; 97]	86 [81; 90]	78 [70; 85]
35–49	98 [98; 98]	94 [93; 95]	90 [88; 91]
50–64	98 [97; 98]	93 [91; 94]	88 [86; 90]
65–74	96 [95; 97]	90 [88; 92]	85 [82; 87]
≥75	93 [91; 95]	85 [81; 89]	82 [76; 86]
Grade			
1	100 [99; 100]	99 [97; 99]	97 [95; 98]
2	99 [98; 99]	95 [94; 96]	91 [89; 93]
3	96 [95; 97]	84 [82; 86]	78 [75; 80]
unknown	95 [93; 96]	87 [85; 89]	82 [79; 84]
Stage			
1	100 [100; 100]	100 [99; 100]	99 [98; 99]
2	98 [98; 99]	93 [91; 94]	86 [84; 88]
3	96 [92; 98]	68 [61; 74]	58 [50; 65]
4	68 [62; 73]	39 [33; 45]	26 [20; 32]
unknown	95 [93; 96]	87 [84; 89]	82 [79; 85]

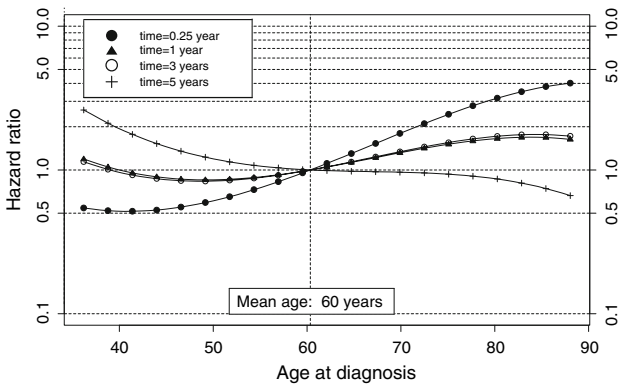

Fig. 1 Hazard ratio according to age at diagnosis (all women)

In women with grade 2, unknown grade, stage 4 or unknown stage, young women were not at higher risk of death. The risk of death increased with age in a linear way in grade 2 and stage 4 tumors. In unknown grade and unknown stage tumors, the risk of death was higher in older women.

Besides, in women with grade 3 tumors, the effect of age depended on the time elapsed since diagnosis. Five years after diagnosis, young women were at higher risk of death than older women although few months after diagnosis the inverse phenomenon was observed.

Figure 3 allowed studying the evolution of the excess mortality rate along the time elapsed since diagnosis by age group, in women with grade 3 tumors. Elderly women

Table 3 Effect of age by grade and stage

	Age effect	Linear/Non-linear	PH/Non-PH
All women	Yes	Non-linear	Non-PH
Grade			
1	No	NA	NA
2	Yes	Linear	PH
3	Yes	Non-linear	Non-PH
Unknown	Yes	Non-linear	PH
Stage			
1	NA	NA	NA
2	NA	Non-linear	PH
3	No	/	/
4	Yes	Linear	PH
Unknown	Yes	Non-linear	PH

NA not available; *PH* proportional effect of age

(≥75) had a high excess mortality rate during the first months follow-up; afterwards, the excess rate decreased over time. In young women (<35), the evolution of the excess mortality rate was very different; it remained constant over time. Thus, the excess mortality rate in women aged <35 matched or even exceeded the rate found in the oldest groups after five years follow-up.

The analysis of relative survivals at 5 years by age group in these women with grade 3 tumors (Fig. 4) showed that the survival of the youngest women (<35) is similar to the one observed in women aged >50 years and lower to than of women aged 35–49.

The effect of age on women with stage 1 tumors could not be explored with our statistical method because of a low mortality rate in that group: the functions did not converge.

In women with stage 2 tumors, age did not seem to have an important effect; moreover, few functions converged and the significant effect of age could not be tested.

Discussion

The present population-based survival study confirmed that young women aged ≤35 had more aggressive breast cancer than other age groups, which is in agreement with previous studies [2, 5, 8–13]: young women had poorly differentiated tumors and more frequently nodal involvement. The bad prognosis in young women could be due to a more aggressive disease. Considering grade and stage separately and introducing age as a continuous covariate, we found no effect of age in women with grade 1, stage 2, or stage 3 tumors. We found an increasing and linear effect of age in women with grade 2 or stage 4 tumors. In all these situations, younger women did not appear at higher risk of death whatever the time elapsed since the diagnosis. In women with grade 3 tumors, a non-linear and non-proportional effect of age was found, resulting in a particular profile of the excess mortality rate: older women were at higher risk at the beginning of the follow-up whereas the inverse phenomenon was observed at five years. However, the five-year cumulative excess mortality rate was finally not lower in youngest women than in women >50 years. Women aged 35–49 had higher 5-year survival than women <35.

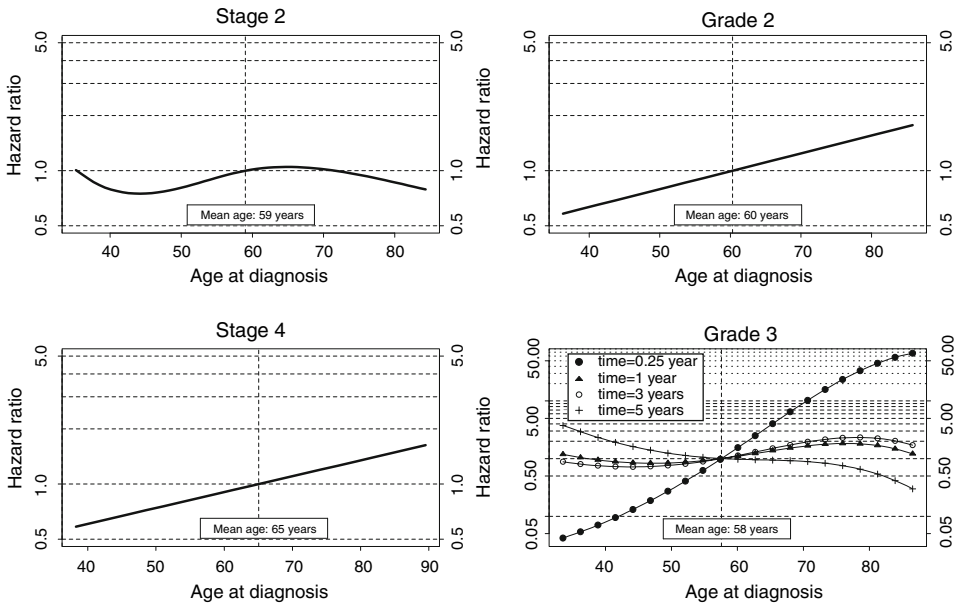

Fig. 2 Hazard ratio according to age at diagnosis by stage (left) and grade (right). Note that the extents of the Y scales for the hazard ratio are different

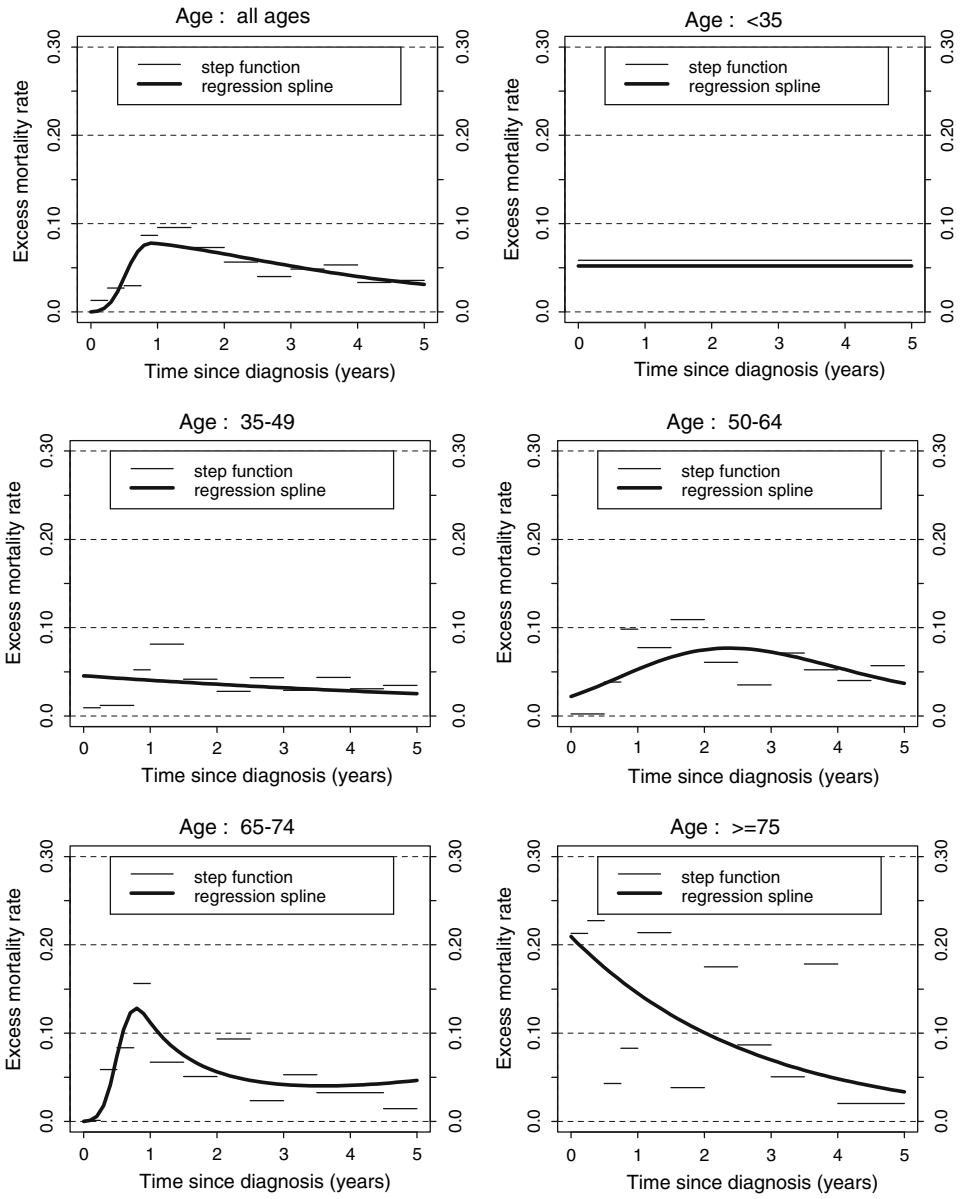

Fig. 3 Evolution of the excess mortality rate with time elapsed since diagnosis by age group in women with grade 3 tumors

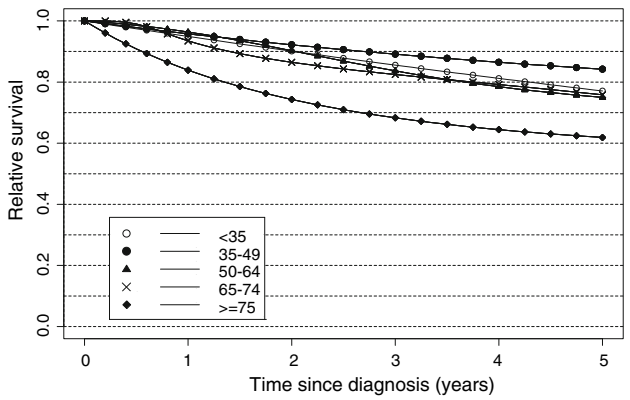

Fig. 4 Relative survival according to the age group in women with grade 3 tumors

In their disease-specific survival analysis [17], Rosenberg et al. used a Cox proportional hazards regression. After adjustment for grade, stage, tumor size, and race, age had a significant effect but violated the proportional hazards assumption. Therefore, their model was stratified on age; thus, the effect of age could not be directly quantified. On the contrary, our statistical approach allowed modeling the effect of age and restricting the number of hypotheses. Cubic splines offered a great flexibility and the non-proportional term [h(t)] allowed releasing the proportional assumption. There was no hypothesis about the relationship between the excess mortality rate and grade or stage and no assumption of additivity was made because separate models were written for each grade and each stage. Age

was considered as a continuous variable; thus, all the available information was used.

The Cancer Registry of Isère allowed taking into account tumor grades and stages, the important predictors of tumor behavior in breast cancer. However, one limitation of our study is the rather high proportion of missing data about grade and stage, especially that survivals of women with unknown grade or stage were not found similar to the survival of the whole population. The fact that missing information on metastasis was considered as "no metastases" is surely debatable; nevertheless, some investigations demonstrated its appropriateness (the proportion of patients with metastasis in our cohort and in other French registry studies is the same [1, 15]).

In agreement with other survival studies [4, 5, 21, 22], we found a poor relative survival in young women 5 years after diagnosis and the best prognosis in women aged 35–49. To deepen exploration of the impact of age, excess mortality rate was modeled according to age as a continuous variable instead of a categorical one. In the whole study population, we found that the effect of age was not linear and that it varied with the time elapsed since diagnosis: few months after diagnosis, age was a negative prognostic factor and became a protective factor five years after diagnosis. The same result has been found using the French cancer registries database [16]. The high mortality rate in old women few months after diagnosis may be due to therapy adverse effects in this fragile category.

In another population-based study [15] Dabakuyo et al. did not confirm the influence of age in multivariate relative survival analysis. They used the database of a breast-cancer-specific registry, which allowed including many covariates collected in routine: age at diagnosis, TNM stage, number of examined nodes, grade, hormone status, period of diagnosis, locoregional extension, and tumor multifocal status. In that study, age at diagnosis was categorized and the younger age group was women under to 45; thus, the effect of a very young age could have been concealed. Nevertheless, many covariates included in that analysis but not included in our model could explain the effect of age; in particular, the hormone receptor status which is an important prognostic factor linked with age [8, 9, 11–13]. Actually, information about hormone receptor status was not available in the present study, because it was not routinely collected by the Cancer Registries of Isère.

The present result are not consistent with previous results by Tai et al. who modeled the effect of age on disease-specific survival in T1 and T2 breast carcinoma [18]; i.e., in tumor sizes <50 mm. They reported a significant quasi-quadratic effect of age, with a lower hazard ratio in women aged 50–60 and an increased risk in older and younger women. Let us note that the latter results were found after adjustment for many tumors characteristics (of which grade, tumor size, and number of positive nodes) and after checking the proportional assumption, which was rejected.

Our results suggest that the particular evolution of excess mortality rate, showing a greater mortality at 5 years for youngest grade 3 women, has no impact in terms of cumulative risk at 5 years in comparison with that of women aged >50 years. However, women aged between 35 and 49 years had a better prognosis. One hypothesis is that more aggressive treatments are usually given to the youngest women. Indeed, during the first years of follow-up, cancer could be well-controlled and therapy adverse effects low. However, five years after diagnosis, treatment morbidity, cancer recurrence, or metastasis may appear in those women. This interpretation would be potentially strengthened if a longer follow-up was available, but it is not supported by the results observed in stage 3 patients who should have experienced the same phenomenon. The fact is that our estimates in women <35 with stage 3 tumors were not accurate because of the small sample size of that group. Otherwise, it could be argued that young women with high-grade tumors would have more frequently a genetic or inherited susceptibility. Actually, familial breast cancers had higher grade than non-familial breast cancers [23, 24] and they affected young women. Hence, a second tumor (contralateral breast cancer, ovarian cancer) or subsequent cancer would appear more frequently in these women. Once again, long-term estimates are needed.

In conclusion, studying the evolution of the annual excess mortality rate according to age at diagnosis in different grade and stage subgroups is possible with appropriate modeling of non-linear and non-proportional effects of age. Youngest women with grade 3 showed a specific evolution of that rate, but that result should be further explored with long-term follow-ups.

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Appendix

Table 4 The five models compared by AIC

Non-linear non-proportional model	$\log(\lambda c) = f(t) + g(a) + h(t)*a$
Non-linear proportional model	$\log(\lambda c) = f(t) + g(a)$
Linear non-proportional model	$\log(\lambda c) = f(t) + \beta*a + h(t)*a$
Linear proportional model	$\log(\lambda c) = f(t) + \beta*a$
Null model	$\log(\lambda c) = f(t)$

λc = excess mortality rate
a = age at diagnosis
t = time elapsed since diagnosis
$f(t)$ and $h(t)$ = cubic splines, knot at one year follow-up;
$g(a)$ = cubic regression spline, knot at the mean age:

$$f(t) = \beta 1^{*}t + \beta 2^{*}t^{2} + \beta 3^{*}t^{3} + \beta 4^{*}t^{3+}$$
$$h(t) = \delta 1^{*}t + \delta 2^{*}t^{2} + \delta 3^{*}t^{3} + \delta 4^{*}t^{3+}$$
$$g(a) = \gamma 1^{*}a + \gamma 2^{*}a^{2} + \gamma 3^{*}a^{3} + \gamma 4^{*}a^{3+}$$

$t^{3+} = (t - 1)^{3}$ when $t > 1$
$t^{3+} = 0$ when $t \leq 1$
$a^{3+} = (a - \text{mean age})^{3}$ when $a >$ mean age at diagnosis
$a^{3+} = 0$ when $a \leq$ mean age at diagnosis

Table 5 Selected models according to AIC

All women	$f(t) + g(a) + h(t)$*a
Grade	
1	$f(t)$
2	$f(t) + \beta$*a
3	$f(t) + g(a) + h(t)$*a
Unknown	$f(t) + g(a)$
Stage	
1	/
2	$f(t) + g(a)$
3	$f(t)$
4	$f(t) + \beta$*a
Unknown	$f(t) + g(a)$

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