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EPIDEMIOLOGY

The prognostic impact of age in patients with triple-negative breast cancer

Cornelia Liedtke · K. R. Hess · T. Karn · A. Rody · L. Kiesel · G. N. Hortobagyi · L. Pusztai · A. M. Gonzalez-Angulo

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Abstract The purpose of this study was to assess the prognostic impact of age in patients with triple-negative breast cancer (TNBC). 1,732 patients with primary TNBC were analyzed. Five age cohorts (≤30, 31–40, 41–50, 51–60, and >60 years) at diagnosis were correlated with clinical/pathological parameters. Univariate and multivariate analyses were used to examine the effect of age on disease-free (DFS), distant disease-free (DDFS), and overall survival (OS). In patients with TNBC, increasing age at diagnosis was inversely correlated with tumor grade ($P < 0.0001$); likelihood of being non-Caucasian ($P = 0.0001$); likelihood of getting chemotherapy ($P < 0.0001$); and positively correlated with DFS ($P = 0.0003$); DDFS ($P < 0.0001$); and OS ($P < 0.0001$). The median DFS for patients 31–40 and older than 60 years was 4 years [95 % confidence interval (95 % CI) 2–5] and 8 years (95 % CI 5–14, respectively, $P = 0.0003$). The DDFS and OS were also statistically significantly shorter for younger patients. In multivariate analysis, tumor size, nodal stage, tumor grade, and age remained significant independent prognostic variables. Clinical characteristics of TNBC differ by age group, patients ≤40 years have poorer survival despite more aggressive systemic therapy.

Keywords Triple-negative breast cancer · Age at diagnosis · Prognosis · Chemotherapy · Survival

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C. Liedtke (✉) · A. Rody
Department of Gynecology and Obstetrics, University of Schleswig–Holstein, Campus Luebeck,
Ratzeburger Allee 160, 23538 Luebeck, Germany
e-mail: cornelia.liedtke@uksh.de

K. R. Hess
Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

T. Karn
Department of Obstetrics and Gynecology, J. W. Goethe-University, Frankfurt, Germany

L. Kiesel
Department of Gynecology and Obstetric, University of Muenster, Muenster, Germany

G. N. Hortobagyi · A. M. Gonzalez-Angulo
Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

L. Pusztai
Breast Medical Oncology, Yale School of Medicine, New Haven, CT, USA

Introduction

Rather than constituting a homogeneous entity, breast cancer is increasingly understood to consist of several breast cancer subgroups [1] that differ with regard to molecular, pathological, and clinical features. The triple-negative breast cancer (TNBC) subtype is characterized by lack of expression of estrogen receptor (ER) and progesterone receptor (PR), as well as lack of overexpression/amplification of the HER2/*neu* oncogene [2]. Patients with TNBC suffer from a generally unfavorable prognosis compared to other breast cancer subtypes, however, a subset of patients is highly sensitive to existing adjuvant/neoadjuvant chemotherapies and have good outcome with therapy [3].

Patient age at the time of diagnosis is an important prognostic factor for breast cancer in general [4]. However, the incidence of different subtypes of breast cancers is

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different across age groups. Cancers that are ER-positive are more frequent in older women, whereas TNBC is relatively more frequent in younger women. It is currently unknown if TNBC that develops in younger women is biologically and clinically different from TNBC in older women. It is also not well-analyzed whether the prognosis of TNBC differs by age at diagnosis. However, previous studies have demonstrated that age may be a prognostic factor for patients in the subtype of patients with TNBC [5] and some have suggested that age is an adverse prognostic factor independent of breast cancer subtype suggesting that breast cancer in young women may represent a distinct entity [6]. However, other studies could not confirm the independent prognostic impact of age in all breast cancer subsets; instead, the prognostic significance of young age was found to depend on molecular subtype. Age of <35 years was a poor prognosticator in all patient subgroups but patients with TNBC [7]. The purpose of this study was to assess clinical and pathological variables across five different non-overlapping age cohorts of TNBC including ages ≤30, 31–40, 41–50, 51–60, and >60 years. We also examined differences in overall survival, disease-free survival, and distant disease-free survival for patients diagnosed with stages I–III TNBC at different ages.

Methods

Study population

Patients who were diagnosed with or treated for triple-negative breast cancer at the M.D. Anderson Cancer Center (Houston, TX) between 1982 and 2008 were included in our study. Patients were selected from the Breast Medical Oncology Clinical Database containing clinical and histological characteristics of all patients that had been obtained from medical records and compiled prospectively.

Patients were selected for inclusion in this study based on the following criteria: diagnosis of primarily non-metastatic breast cancer, lack of expression of ER, PR, lack of overexpression/amplification of HER2, and female sex. Exclusion criteria included male sex, primary metastatic breast cancer as well as lack of information regarding ER, PR, and/or HER2 status.

Based on their age at diagnosis, patients were stratified into five distinct categories [≤30 ($N = 63$), 31–40 ($N = 303$), 41–50 ($N = 528$), 51–60 ($N = 503$), and >60 years ($N = 335$)]. Staging was performed according to the American Joint Committee on Cancer [8] guidelines valid for each time period. To demonstrate that staging inconsistencies according to varying classifications over time did not influence our results, we analyzed the distribution of age in 5-year time periods. This would allow us to exclude a bias through stage migration (due to use of different classification systems) that corresponds to age. The Spearman rank correlation coefficient between age at diagnosis and 5-year period was 0.12 with a P value of 0.0001 demonstrating a very modest positive correlation. The median age at diagnosis prior to 1995 was 44, the median age from 1995 to 2000 was 49, the median age from 2000 to 2005 was 50, and the median age from 2005 to 2009 was 51. This effect does not seem to have influenced our results substantially.

No central pathology review was performed for this analysis; however, all primary tumors had been reviewed by a dedicated breast pathologist on first referral to MDACC. This data analysis was approved by the MDACC institutional review board. Also, the MDACC institutional review board approved an informed consent waiver in retrospective chart review-based analyses such as presented in this manuscript.

Pathology assessment

ER and PR status had been determined using immunohistochemistry (IHC) for ER and PR (IHC, 6F11 and 1A6 Novacastra Laboratories Ltd, Burlingame, CA); HER2 status was evaluated using fluorescence-in situ-hybridization (FISH) or IHC (Dako North America Inc, Carpinteria, CA). For cases diagnosed at MDACC, the thresholds for ER and/or PR positivity were defined as nuclear staining of less than 10 % of tumor cells. HER2 positivity was defined as either HER2 gene amplification (FISH) or an IHC score of 3. For patients from outside MDACC, cases were reviewed by dedicated breast pathologists and assays were repeated if found to have inadequate quality. Nuclear grading was classified based on Black's-modified grading system [9].

For patients who received neoadjuvant therapy, the extent of residual cancer was determined through histological evaluation of the excised tumor bed and lymph nodes, and response was dichotomized as pathologic complete response (pCR, i.e., lack of invasive breast cancer cells in both breast tissue and lymph node) versus residual disease (RD, i.e., any invasive cancer). Patients with residual non-invasive breast cancer (e.g., DCIS) at the time of surgery were also classified as pCR [10].

Statistical analysis

Univariate correlation analysis was performed between the above age cohorts at diagnosis and the following variables; T size (pT0–pT4), N stage (pN0–pN3), nuclear grade (grades 1–3), ethnicity (Asian Pacific, Black American, Native American, Caucasian, Hispanic, and other), receipt of neoadjuvant or adjuvant chemotherapy (yes vs. no),

response to neoadjuvant chemotherapy (pCR vs. RD), type of chemotherapy regimen (none, anthracycline, anthracycline–taxane combination, CMF, taxane, and other), and family history of breast cancer (0, 1, or ≥2 additional family members with breast cancer) based on Spearman's rank correlation and Kruskal–Wallis test, using age without categorization to increase statistical power.

Overall survival was defined as the time between date of diagnosis and last follow-up or death from any cause. Disease-free survival (DFS) was measured from the date of diagnosis to diagnosis of local, regional or distant recurrence, last patient contact, or patient death. Distant disease-free survival (DDFS) was defined as the time interval between the date of diagnosis and diagnosis of distant disease or last patient follow-up or patient death of any cause.

The Kaplan–Meier method was used to estimate survival time distributions. A univariate Cox proportional hazards model was used to evaluate the influence of age and other covariates on outcomes. Multivariate survival analysis was performed using Cox proportional hazards regression analysis as a model including tumor size (*T*0–2 vs. *T*3–4), nodal status, and administration of adjuvant chemotherapy, grade, family history, and age at diagnosis (i.e., age > 40 vs. ≤ 40 years). All *P* values were two-sided.

For statistical analysis, S-PLUS® 8.0 for Windows (Insightful Corp.) was used.

Results

Patient characteristics

The total study population consisted in 1,732 patients with triple-negative breast cancer (Table 1). After 7,315 person years of follow-up, there were 541 deaths. The median OS was 9.6 years (95 % CI 8.3–11.8). Survival probabilities were 98 % at 1 year, 78 % at 3 years, 66 % at 5 years, 49 % at 10 years, 34 % at 15 years, and 30 % at 20 years. The majority of patients received some form of adjuvant/neoadjuvant systemic cytotoxic therapy.

Correlation analysis

The results of correlation analysis between age at diagnosis and clinical/pathological variables are presented in Table 2. Younger patients with TNBC were more often diagnosed with grade 3 tumors (i.e., patients aged 31–40 and >60 years had 93 and 83 %, respectively, $P < 0.0001$). We also found significant associations between nodal stage, ethnicity, and age at diagnosis.

With regard to systemic therapy, patients with TNBC who were diagnosed at age ≤30 or 31–40 years received neoadjuvant (38 and 35 vs. 26 %) or adjuvant (65 and 61 vs. 43 %) chemotherapy significantly more frequently than patients older than 60 ($P = 0.0012$ and $P < 0.0001$, respectively). Among the patients who received adjuvant chemotherapy, patients ≤30 years at diagnosis were significantly more likely to receive an anthracycline-containing combination chemotherapy compared to patients aged >60 years (44 vs. 29 %, $P < 0.0001$). No significant associations were observed for age at diagnosis and either tumor stage or family history. Pathologic response rates were also similar across age groups.

Univariate survival analysis

Overall 737 DFS events (541 deaths and 196 recurrences) were observed. There was a significant correlation between age at diagnosis and DFS (likelihood ratio $P = 0.0003$). 5-year DFS was 40, 42, 56, 57, and 57 % for patients aged ≤30, 31–40, 41–50, 51–60, and >60 years, respectively. Median DFS for patients aged 31–40 years was 4 years (95 % CI 2–5), whereas it was 8 years (95 % CI 5–14) and 7 years (95 % CI 6–not reached) for patients aged 41–50 or 51–60 years at time of diagnosis, respectively (Table 3 and Fig. 1a).

A similarly significant effect regarding age at diagnosis and DDFS was observed. There were 597 distant recurrences with a median time to distant recurrence of 10.0 years (95 % confidence interval 7.8–15.2 years). The 5-year freedom from distant recurrence probabilities were 46, 48, 62, 65, and 70 % for patients aged ≤30, 31–40, 41–50, 51–60, >60 years (likelihood ratio $P < 0.0001$). Analysis again showed that patients aged 31–40 years compared to patients aged 41–50 or 51–60 years had significantly decreased median DDFS [5 years (95 % CI 4–6) versus 9 years (95 % CI 8–not reached) and 15 years (95 % CI 14–not reached), respectively], Table 3 and Fig. 1b.

In analysis regarding OS again a significant effect of age on prognosis could be demonstrated. The 5-year survival probabilities were 59, 53, 60, 69, and 64 % for patients aged ≤30, 31–40, 41–50, 51–60, and >60 years (likelihood ratio $P < 0.0001$) ($P = 0.0074$, Table 3; Fig. 1c).

To estimate how the median DFS and OS changed with age, we employed a moving average smoothing function that uses weighted Kaplan–Meier estimates of the median DFS, DDFS, and OS. We estimated point-wise 95 % confidence intervals using the bootstrap method (Fig. 2a–c). The estimated median DFS was 3.5 years at age 30, 5.3 at 40, 7.5 at 50, 7.4 at 60, 7.8 at 70, and 7.9 at 80. Figure 2a suggests a piece-wise linear effect of age on survival, with a join-point between the two pieces at about 50 years of age. Therefore, such a function was fitted to the data using Cox proportional hazards regression analysis. Testing the

Table 1 Clinical and pathological as well as treatment characteristics of the study population

	N	%
Age groups		
≤30 years	63	3.6
31–40 years	303	17.5
41–50 years	528	30.5
51–60 years	503	29.0
>60 years	335	19.4
T stage		
0	182	10.7
1	793	46.5
2	573	33.6
3	94	5.5
4	65	3.8
Unknown	25	–
N stage		
0	1,027	60.5
1	523	30.8
2	90	5.3
3	57	3.4
Unknown	35	–
Nuclear grade		
1	12	0.7
2	155	9.3
3	1,507	90.0
Unknown	58	–
Ethnicity		
Asian Pacific	54	3.12
Black American	303	17.5
Native American	4	0.2
Other	18	1.0
Hispanic	217	12.5
Caucasian	1,136	65.6
Neoadjuvant chemotherapy		
No	1,183	68.3
Yes	549	31.7
Response to neoadjuvant chemotherapy		
pCR	148	27.0
RD	401	73.0
Not applicable	1,183	–
Adjuvant chemotherapy		
No	596	37.9
Yes	1,076	62.1
Adjuvant chemotherapy regimen		
None	596	–
Anthracycline	339	32.2
Anthracycline/taxane	524	49.8
CMF	61	5.8
Other	19	1.8
Taxane	110	10.5
Unknown	83	–
Family history of breast cancer (i.e. no of family members with known breast cancer)		
0	964	55.7
1–2	635	36.6
≥3	133	7.7

piece-wise linear proportional hazards model against a simple linear proportional hazards model yielded a *P* value of 0.039. The estimated median time to distant recurrence was 5.0 years at age 30, 7.3 at 40, 11.5 at 50, 14.0 at 60, 16.2 at 70, and 15.8 at 80. Figure 2b also suggested a piece-wise linear effect of age on DDFS. Testing the piece-wise linear proportional hazards model against a simple linear proportional hazards model however, yields a non-significant *P* value of 0.25. The estimated median OS was 6.9 years at age 30, 8.8 at 40, 10.6 at 50, 10.8 at 60, 10.7 at 70, and 10.8 at 80. Again, Fig. 2c suggested a piece-wise linear effect of age on survival. Testing the piece-wise linear proportional hazards model against a simple linear proportional hazards model yields a *P* value of 0.076.

Multivariate survival analysis

In multivariate analysis for DFS, DDFS, and OS, including age (≤40 vs. >40 years), family history of breast cancer, nuclear grade, tumor size, and nodal status as variables, all variables except family history of breast cancer were significantly and independently associated with prognosis. The hazard ratio (HR) for recurrence was 0.68 (95 % CI 0.58–0.81) for patients >40 compared to ≤40 years of age, this implies an approximately 30 % greater risk for recurrence among younger patients ($P < 0.0001$, Table 4). Similarly, the corresponding HR for death was 0.70 (95 % CI 0.58–0.86, $P < 0.0001$).

Discussion

In this study, we demonstrate in a large dataset of 1,732 patients with TNBC that young age at diagnosis is an important unfavorable prognostic factor even in the presence of systemic adjuvant/neoadjuvant chemotherapy. The unfavorable effect of young age at diagnosis on DFS was independent of nodal status, tumor diameter, and tumor grade, and family history of breast cancer and could be observed despite an increased likelihood of receiving both neoadjuvant and/or adjuvant chemotherapy. However,

Table 2 Results of the correlation analysis between age at diagnosis and clinical/pathological variable in patients with triple-negative breast cancer (column percentages are given in brackets)

	≤30 years *N* (%)	31–40 years *N* (%)	41–50 years *N* (%)	51–60 years *N* (%)	>60 years *N* (%)	*P* value[c]
T stage[a]						
0	7 (11)	36 (12)	62 (12)	50 (10)	27 (8)	0.42
1	25 (41)	120 (41)	242 (46)	234 (47)	172 (52)	
2	26 (43)	109 (37)	162 (31)	167 (34)	109 (33)	
3	2 (3)	17 (6)	38 (7)	20 (4)	17 (5)	
4	1 (2)	13 (4)	17 (3)	26 (5)	8 (2)	
N stage[a]						
0	35 (56)	173 (58)	298 (57)	314 (64)	207 (64)	0.036
1	26 (41)	97 (33)	177 (34)	140 (29)	83 (26)	
2	2 (3)	17 (6)	24 (5)	22 (4)	25 (8)	
3	0 (0)	9 (3)	24 (5)	14 (3)	10 (3)	
Nuclear grade[a]						
1	0 (0)	1 (0)	1 (0)	5 (1)	5 (2)	<0.0001
2	4 (7)	18 (6)	38 (7)	43 (9)	52 (16)	
3	56 (93)	271 (93)	473 (92)	438 (90)	279 (83)	
Ethnicity						
Asian pacific	2 (3)	15 (5)	16 (3)	14 (3)	7 (2)	0.0001
Black	2 (14)	52 (17)	97 (18)	90 (18)	55 (16)	
Native American	0 (0)	0 (0)	2 (0)	1 (0)	1 (0)	
Other	1 (2)	5 (2)	5 (1)	5 (1)	2 (1)	
Spanish	14 (22)	54 (18)	69 (13)	49 (10)	31 (9)	
Caucasian	37 (59)	177 (58)	339 (64)	344 (68)	239 (71)	
Neoadjuvant chemotherapy						
No	39 (62)	196 (65)	354 (67)	346 (69)	248 (74)	0.0012
Yes	24 (38)	107 (35)	174 (33)	157 (31)	87 (26)	
Response to neoadjuvant chemotherapy[b]						
pCR	5 (21)	32 (30)	50 (29)	40 (25)	21 (24)	0.79
RD	19 (79)	75 (70)	124 (71)	117 (75)	66 (76)	
Adjuvant chemotherapy						
No	20 (32)	100 (33)	181 (34)	178 (35)	117 (53)	<0.0001
Yes	43 (68)	203 (67)	347 (66)	325 (65)	158 (47)	
Adjuvant chemotherapy regimen ($N = 953$)						
Anthracycline	19 (44)	65 (32)	99 (29)	111 (35)	45 (29)	<0.0001
Anthracycline/taxane combination	17 (40)	102 (51)	181 (54)	153 (48)	71 (46)	
CMF	3 (7)	7 (3)	15 (4)	19 (6)	17 (11)	
Taxane	3 (7)	25 (12)	31 (9)	34 (11)	17 (11)	
Other	1 (2)	2 (1)	10 (3)	3 (1)	3 (2)	
Family history of breast cancer (i.e., no. of family members with known breast cancer)						
0	33 (52)	160 (53)	292 (55)	285 (57)	194 (58)	0.057
1–2	23 (37)	117 (39)	190 (36)	187 (37)	118 (35)	
≥3	7 (11)	26 (9)	46 (9)	31 (6)	23 (7)	

RD residual invasive breast cancer after completion of neoadjuvant chemotherapy, *pCR* pathological complete response (i.e., absence of invasive breast cancer in the breast and axillary lymph nodes) after completion of neoadjuvant chemotherapy

[a] Percentages are based on different column totals for each variable depending on the amount of missing data

[b] Neoadjuvant response was determined for all 549 patients undergoing neoadjuvant chemotherapy

[c] Based on Spearman's rank correlation analysis (for *T* size, *N* stage, grade) and Kruskal–Wallis test (or race, treatments characteristics, and family history) using age without categorization

Table 3 Median disease-free, distant disease-free, and overall survival in distinct age groups

	DFS			DDFS		OS	
	N	Median (years)	95 % CI	Median (years)	95 % CI	Median (years)	95 % CI
≤30 years	63	4	2–NR	4	3–NR	7	4–NR
31–40 years	303	4	2–5	5	2–5	7	5–8
41–50 years	528	8	5–14	9	8–NR	12	8–13
51–60 years	503	7	6–NR	15	14–NR	14	8–NR
>60 years	335	7	5–11	17	11–NR	10	9–NR

NR not reached

larger tumor size, nodal positivity, and high nuclear grade remained significant and independent poor prognostic variables for TNBC. The largest absolute difference was observed between patients younger than 40 and patients aged 41 or older. Also, while the majority of neighboring confidence intervals overlapped, there was a significant difference regarding DFS between patients aged 31–40 years [median DFS 4 years (95 % CI 2–5)] and 41–50 years of age (median DFS 8 years 95 % CI 5–12) at the time of diagnosis. Similar effects could be observed for DDFS and OS. Given the fact that the adverse prognosis observable among patients of young age outweighed the competing death risks in the older population aged we hypothesize a strong adverse effect of young age at diagnosis (i.e., ≤40 years) on prognosis in patients with TNBC.

It is widely recognized that increasing age constitutes an important favorable prognostic factor for breast cancer in general. However, it has been demonstrated that age-dependent differences in prognosis may be due to differences in the distribution of breast cancer subtypes across age groups [11]. The more favorable prognosis of older patients is at least partly due to the greater incidence of ER-positive, luminal A cancers in this age group [3, 12, 13]. In this study, we evaluated the prognostic effect of age in a uniform patient subset of triple-negative breast cancers.

In the current literature, there is limited and conflicting data with regard to the prognostic impact of age in patients with triple-negative breast cancer. In a previous study of patients with metastatic triple-negative breast cancer, age at diagnosis less than 50 years was an independent adverse prognostic factor in multivariate analysis [14]. Similarly, a recent analysis of 375 patients with stage I breast cancer (T1a: 93, T1b: 162, T1mic: 120) showed that both ages younger than 35 years (HR 4.91; 95 % CI 1.014–23.763, $P = 0.048$) and diagnosis of a triple-negative phenotype (HR 4.93; 95 % CI 1.312–18.519, $P = 0.018$) were significantly associated with a higher rate of recurrence [15]. However, in a recent analysis from Japan, Yoshida and colleagues analyzed a cohort of patients under the age of 40. In this analysis, independent factors associated with poor disease-free survival and overall survival included positive axillary lymph nodes and triple-negative status, but not age at diagnosis. The authors suggest that other clinical and pathological features rather than age should be used to determine individualized treatment courses for breast cancer patients younger than 40 years [16].

In our analysis, patients with younger age showed a significantly higher rate of high grade tumors ($P < 0.0001$). This higher incidence of high grade tumors among younger TNBC patients may to some extent explain the unfavorable prognosis; however, in multivariate analysis taking into account both grade and age, age at diagnosis remained a significant independent predictor of prognosis.

The adverse effect of young age on prognosis is even more striking considering that younger patients (<40 years) were more likely to receive adjuvant and/or neoadjuvant chemotherapy compared to older patients. Neoadjuvant chemotherapy was given to 38 % of patients ≤30 years and to 35 % of patients 31–40 years compared to 26 % among patients aged >60 years ($P = 0.0012$). Adjuvant chemotherapy was given to 68 % of patients ≤30 years and to 61 % of patients 31–40 years compared to 43 % among patients aged >60 years ($P < 0.0001$). Among those patients who received neoadjuvant chemotherapy, younger patients (i.e., aged ≤30 and 31–40) were more likely to receive anthracycline-containing chemotherapy compared to patients older than 60 (44 and 32 vs. 29 %). This is consistent with physicians' awareness that younger patients are at higher risk for relapse and require aggressive adjuvant therapy. Interestingly, pathologic complete response rates did not differ across age cohorts and ranged from 21 to 30 % ($P = 0.87$).

A potential confounder in our analysis relates to imprecision in ER determination. The accuracy of immunohistochemical assessment of hormone receptor and HER2 status is limited with discordance rates between local and central testing ranging from 10 to 20 % [17, 18]. The rate of testing error is likely to be independent of the age of the patient but the true incidence of ER-positive cancers is increasing with age. Therefore, it is plausible that the rate of false negative ER results is higher among

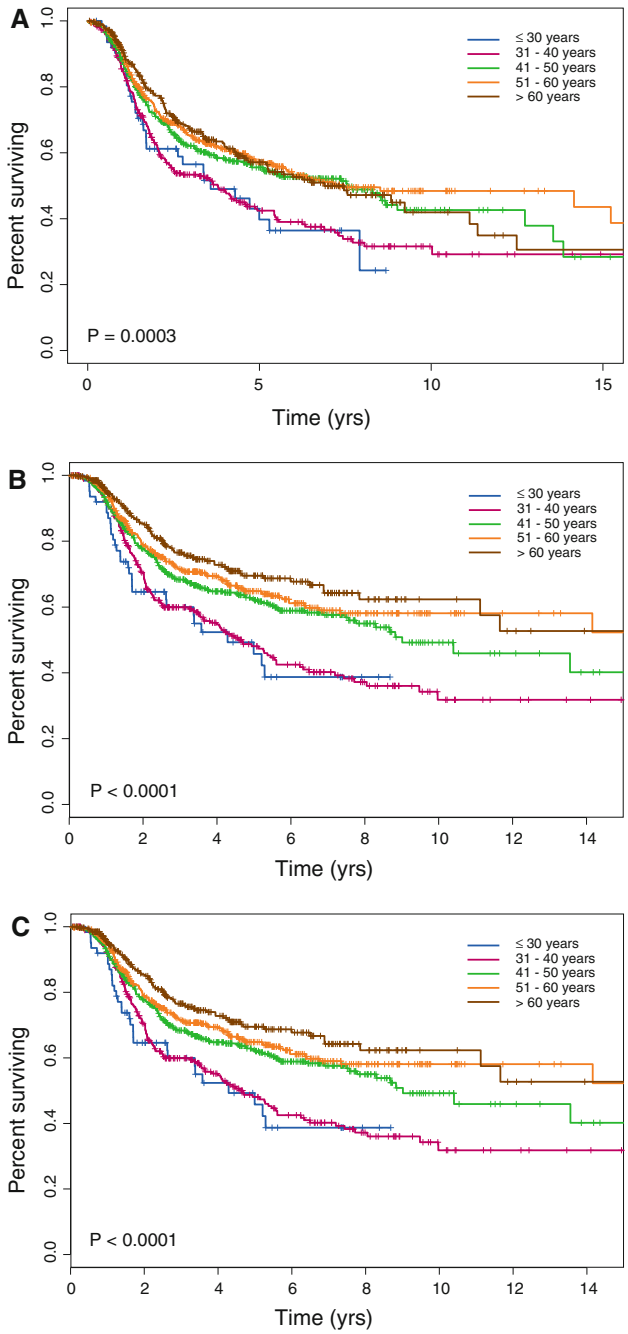

Fig. 1 **a** Disease-free survival in patients with triple-negative breast cancer stratified by patient age. **b** Distant disease-free survival in patients with triple-negative breast cancer stratified by patient age. **c** Overall survival in patients with triple-negative breast cancer stratified by patient age

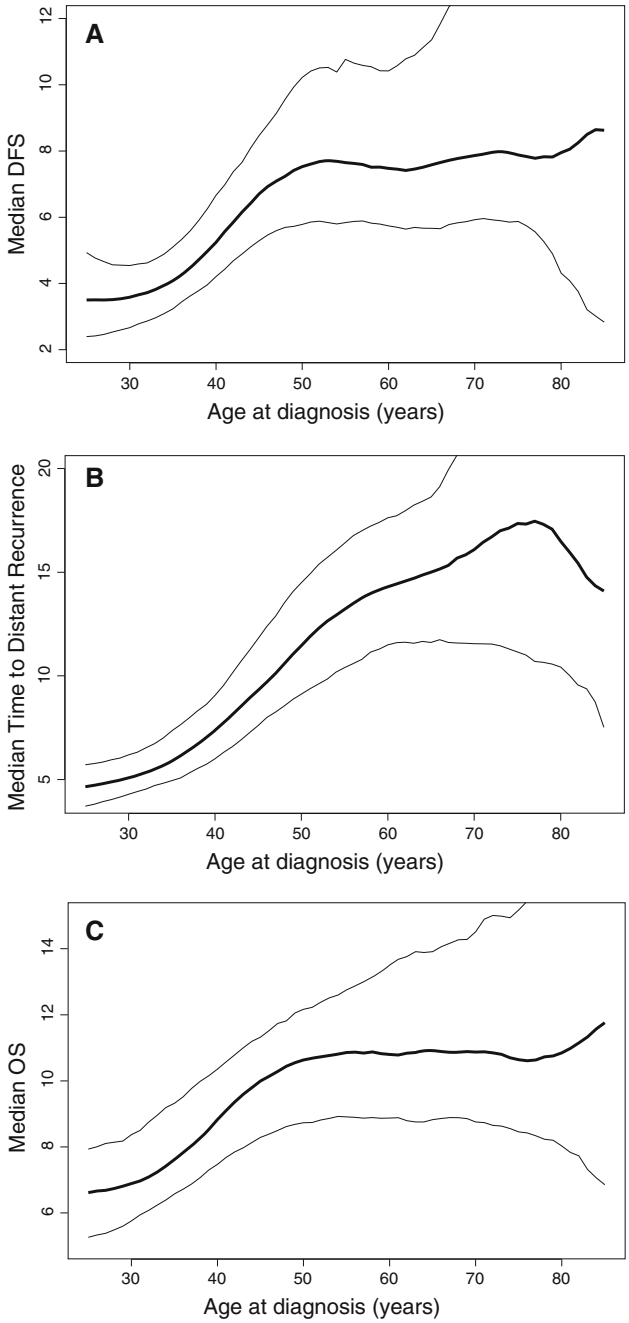

Fig. 2 **a** Moving average smoothing function of weighted Kaplan–Meier estimates for median DFS. Point-wise 95 % confidence intervals were estimated using the bootstrap method. **b** Moving average smoothing function of weighted Kaplan–Meier estimates for median DDFS. Point-wise 95 % confidence intervals were estimated using the bootstrap method. **c** Moving average smoothing function of weighted Kaplan–Meier estimates for median OS. Point-wise 95 % confidence intervals were estimated using the bootstrap method

older patients. This would lead to a greater "contamination" of the older TNBC cohort with some ER-positive patients who are erroneously assigned to ER-negative status compared to the younger age cohorts. ER-positive breast cancers have distinct clinical course compared to ER-negative cancers even in the absence of adjuvant endocrine therapy, particularly the rate of recurrences has a more prolonged tail with many late recurrences compared to true TNBC that has almost all recurrences within the first 5-year of follow-up. Therefore, higher rates of false

Table 4 Results of multivariate analysis including age, family history of breast cancer, nuclear grade, *T* stage, *N* stage for DFS, DDFS, and OS

	HR	95 % CI	*P* value
DFS			
Age[a]	0.68	0.58–0.81	<0.0001
Family history of breast cancer[b]	0.92	0.69–1.23	0.58
Nuclear grade[c]	1.34	1.03–1.74	0.029
T stage[d]	2.02	1.63–2.52	<0.0001
N stage[e]	2.15	1.84–2.51	<0.0001
DDFS			
Age[a]	0.60	0.50–0.73	<0.0001
Family history of breast cancer[b]	0.84	0.60–1.17	0.30
Nuclear grade[c]	1.44	1.06–1.96	0.019
T stage[d]	1.97	1.55–2.51	<0.0001
N stage[e]	2.41	2.02–2.87	<0.0001
OS			
Age[a]	0.70	0.58–0.86	<0.0001
Family history of breast cancer[b]	0.96	0.69–1.33	0.81
Nuclear grade[c]	1.70	1.22–2.36	0.0015
T stage[d]	2.08	1.62–2.66	<0.0001
N stage[e]	2.20	1.84–2.64	<0.0001

[a] Dichotomized as >40 versus age ≤40 years

[b] Dichotomized as 0 or 1 versus ≥2 additional family members with known breast cancer)

[c] Dichotomized as nuclear grades 1 and 2 versus nuclear grade 3

[d] Dichotomized as *T* stages 0−2 versus 3–4

[e] Dichotomized as *N* stage 0 versus 1–3

negative ER results among the older age cohort may contribute to some extent to the better DFS, however, we expect this confounding effect to be very small.

Conclusion

Clinical characteristics of patients with TNBC differ by age groups. Patients aged ≤40 years have poorer survival despite more aggressive systemic therapy. It is increasingly recognized that triple-negative breast cancer is a clinically and molecularly heterogeneous entity with substantial diversity in response to (neoadjuvant) chemotherapy, survival [3] and mutation status in key genes including p53 and BRCA1 [19]. Our findings suggest that the clinical characteristics and in particular the prognosis of early onset and late onset TNBC are different. It will be important for future studies to examine the biological differences that underlie the distinct prognosis of TNBC in younger women compared to older women; these studies may eventually lead to novel and more effective therapies.

Conflict of interest The authors have declared no conflict of interest.

References

1. Perou CM, Sorlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, Pollack JR, Ross DT, Johnsen H, Akslen LA et al (2000) Molecular portraits of human breast tumours. Nature 406(6797): 747–752
2. Gluz O, Liedtke C, Gottschalk N, Pusztai L, Nitz U, Harbeck N (2009) Triple-negative breast cancer—current status and future directions. Ann Oncol 20(12):1913–1927
3. Liedtke C, Mazouni C, Hess KR, Andre F, Tordai A, Mejia JA, Symmans WF, Gonzalez-Angulo AM, Hennessy B, Green M et al (2008) Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol 26(8):1275–1281
4. Aleskandarany MA, Green AR, Benhasouna AA, Barros FF, Neal K, Reis-Filho JS, Ellis IO, Rakha EA (2012) Prognostic value of proliferation assay in the luminal, HER2-positive, and triple-negative biologic classes of breast cancer. Breast Cancer Res 14(1):R3
5. Fredholm H, Eaker S, Frisell J, Holmberg L, Fredriksson I, Lindman H (2009) Breast cancer in young women: poor survival despite intensive treatment. PLoS ONE 4(11):e7695
6. Azim HA Jr, Michiels S, Bedard PL, Singhal SK, Criscitiello C, Ignatiadis M, HaibeKains B, Piccart MJ, Sotiriou C, Loi S (2012) Elucidating prognosis and biology of breast cancer arising in young women using gene expression profiling. Clin Cancer Res 18(5):1341–1351
7. Kim EK, Noh WC, Han W, Noh DY (2011) Prognostic significance of young age (<35 years) by subtype based on ER, PR, and HER2 status in breast cancer: a nationwide registry-based study. World J Surg 35(6):1244–1253
8. Singletary SE, Allred C, Ashley P, Bassett LW, Berry D, Bland KI, Borgen PI, Clark G, Edge SB, Hayes DF et al (2002) Revision of the American Joint Committee on Cancer staging system for breast cancer. J Clin Oncol 20(17):3628–3636
9. Fisher B, Redmond C, Fisher ER, Caplan R (1988) Relative worth of estrogen or progesterone receptor and pathologic characteristics of differentiation as indicators of prognosis in node negative breast cancer patients: findings from National Surgical Adjuvant Breast and Bowel Project Protocol B-06. J Clin Oncol 6(7):1076–1087
10. Mazouni C, Peintinger F, Wan-Kau S, Andre F, Gonzalez-Angulo AM, Symmans WF, Meric-Bernstam F, Valero V, Hortobagyi GN, Pusztai L (2007) Residual ductal carcinoma in situ in patients with complete eradication of invasive breast cancer after neoadjuvant chemotherapy does not adversely affect patient outcome. J Clin Oncol 25(19):2650–2655
11. Bayraktar S, Hernadez-Aya LF, Lei X, Meric-Bernstam F, Litton JK, Hsu L, Hortobagyi GN, Gonzalez-Angulo AM (2012) Effect of metformin on survival outcomes in diabetic patients with triple receptor-negative breast cancer. Cancer 118(5):1202–1211
12. Sorlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, Hastie T, Eisen MB, van de Rijn M, Jeffrey SS et al (2001) Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci USA 98(19):10869–10874
13. Carey LA, Dees EC, Sawyer L, Gatti L, Moore DT, Collichio F, Ollila DW, Sartor CI, Graham ML, Perou CM (2007) The triple negative paradox: primary tumor chemosensitivity of breast cancer subtypes. Clin Cancer Res 13(8):2329–2334

14. Kassam F, Enright K, Dent R, Dranitsaris G, Myers J, Flynn C, Fralick M, Kumar R, Clemons M (2009) Survival outcomes for patients with metastatic triple-negative breast cancer: implications for clinical practice and trial design. Clin Breast Cancer 9(1):29–33
15. Bayraktar S, Gutierrez-Barrera AM, Liu D, Tasbas T, Akar U, Litton JK, Lin E, Albarracin CT, Meric-Bernstam F, Gonzalez-Angulo AM et al (2011) Outcome of triple-negative breast cancer in patients with or without deleterious BRCA mutations. Breast Cancer Res Treat 130(1):145–153
16. Brufsky A, Valero V, Tiangco B, Dakhil S, Brize A, Rugo HS, Rivera R, Duenne A, Bousfoul N, Yardley DA (2012) Second-line bevacizumab-containing therapy in patients with triple-negative breast cancer: subgroup analysis of the RIBBON-2 trial. Breast Cancer Res Treat 133(3):1067–1075
17. Perez EA, Suman VJ, Davidson NE, Martino S, Kaufman PA, Lingle WL, Flynn PJ, Ingle JN, Visscher D, Jenkins RB (2006) HER2 testing by local, central, and reference laboratories in specimens from the North Central Cancer Treatment Group N9831 intergroup adjuvant trial. J Clin Oncol 24(19):3032–3038
18. Pusztai L, Viale G, Kelly CM, Hudis CA (2010) Estrogen and HER-2 receptor discordance between primary breast cancer and metastasis. Oncologist 15(11):1164–1168
19. Gonzalez-Angulo AM, Timms KM, Liu S, Chen H, Litton JK, Potter J, Lanchbury JS, Stemke-Hale K, Hennessy BT, Arun BK et al (2011) Incidence and outcome of BRCA mutations in unselected patients with triple receptor-negative breast cancer. Clin Cancer Res 17(5):1082–1089