Somatic mutations in breast and serous ovarian cancer young patients: a systematic review and meta-analysis

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Summary

Objective: our aim was to evaluate whether somatic mutations in five genes were associated with an early age at presentation of breast cancer (BC) or serous ovarian cancer (SOC).
Methods: COSMIC database was searched for the five most frequent somatic mutations in BC and SOC. A systematic review of PubMed was performed. Young age for BC and SOC patients was set at ≤35 and ≤40 years, respectively. Age groups were also classified in <30years and every 10 years thereafter.
Results: twenty six (1,980 patients, 111 younger) and 16 studies (598, 41 younger), were analyzed for BC and SOC, respectively. In BC, *PIK3CA* wild type tumor was associated with early onset, not confirmed in binary regression with estrogen receptor (ER) status. In HER2-negative tumors, there was increased frequency of *PIK3CA* somatic mutation in older age groups; in ER-positive tumors, there was a trend towards an increased frequency of *PIK3CA* somatic mutation in older age groups. *TP53* somatic mutation was described in 20% of tumors from both younger and older patients; *PTEN*, *CDH1* and *GATA3* somatic mutation was investigated only in 16 patients and *PTEN* mutation was detected in one of them. In SOC, *TP53* somatic mutation was rather common, detected in more than 50% of tumors, however, more frequently in older patients.
Conclusion: frequency of somatic mutations in specific genes was not associated with early-onset breast cancer. Although very common in patients with serous ovarian cancer diagnosed at all ages, *TP53* mutation was more frequently detected in older women.

Keywords: breast neoplasms, ovarian neoplasms, young adult, mutation.

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Introduction

The probability of being diagnosed with an invasive cancer increases with age. In breast cancer, the incidence goes from 1.9%, in women below 50 years, to 2.3, 3.5 and 6.7% in women categorized within the age groups of 50 to 59, 60 to 69 and 70 and over, respectively.[1] Age-specific incidence rates for epithelial ovarian cancer (per 100,000 women) also increase with advancing age, varying from 12.51 to 41.96 and 54.95 in the age groups of 40-44, 60-64 and 75-79 years old.[2] One reason for the increased incidence rate of cancer at older ages is that carcinogenesis is a continuous process associated with the accumulation of genetic and epigenetic damage to the DNA, that takes place along a lifetime.[3]

Although breast cancer is the first leading cause of cancer death in females aged 20 to 59, in adolescents and younger adults, aged 15-39 years, there is still a paucity of information, concerning cancer incidence and behavior. In this age group, breast cancer is the most common type of cancer, responsible for 14% of the cases.[1,4] Younger age has been associated with a less favorable prognosis, which might be in part due to a lower proportion of

luminal A and higher proportion of triple negative and high grade tumors.[5] However, molecular studies have also suggested that breast cancer in young patients may be characterized by unique disease biology, as compared to older patients, beyond subtype distribution.[6]

One of the predisposing factors for breast cancer is germline mutation in tumor suppressor genes such as *BRCA1/2*. In younger patients its frequency may be as high as 10.9 to 23%, as reported in women from different countries.[7-12]

Another cancer associated with *BRCA1/2* germline mutation is epithelial ovarian cancer, where prevalence of the mutation in unselected patients is higher than in breast cancer, varying from 8-13%.[13] In this cancer, high prevalence (24%) was described in women diagnosed in their forties with a lower prevalence in younger women in their thirties (11%).[14] Epithelial ovarian cancer is not common in women below 40 years, and young age has been reported as a favorable prognostic factor. In analogy with older ovarian cancer patients, serous ovarian cancer is the most frequent histology in young women ≤ 40 years, but in contrast, low tumor grade is more common in this age group.[15]

However, *BRCA1/2* germline mutation does not explain breast or epithelial ovarian cancer development in the majority of cases. A large number of cancer somatic alterations were recently characterized, most of which deposited in the COSMIC database (Catalogue of Somatic Mutation in Cancer – http://www.sanger.ac.uk/genetics/CGP/cosmic/).[16] Nevertheless, it is still not clear whether there might be any association between gene somatic mutations and age of diagnosis. Hence, we performed a systematic review and meta-analysis to evaluate a possible association between somatic alterations in specific genes in breast and serous ovarian cancer samples and age at cancer diagnosis.

Methods

Study eligibility and identification

At first, the COSMIC database was searched for the identification of five of the genes most frequently mutated (somatic mutations) in breast cancer, namely *PIK3CA* (25%), *TP53* (23%), *CDH1* (11%), *GATA3* (7%) and *PTEN* (5%). Search strategy was: breast tissue, subtissue (all), cancer histology, subhistology (all). Date References shown in COSMIC for these selected genes were reviewed. The search was performed on October 2013.

A literature search through PubMed database followed, to ensure that studies including somatic alterations in these specific genes in breast cancer were not missed. PubMed was searched for using the key words specified: breast neoplasms [MeSH terms] AND "somatic" [all fields] AND ("2003/10/13" [PDat]: "2015/02/11" [PDat] AND "humans" [MeSH terms]) and (breast neoplasm [MeSH terms]) AND "somatic") AND "*PIK3CA*"; followed by *TP53*; *P53*; *CDH1*; *GATA3* and *PTEN*. After consulting COSMIC and PubMed, a total of 821 unique articles were identified. After exclusions, which were mainly due to lack of individual data for age or gene mutation, 26 studies were selected (Table 1).

The same strategy used above was employed to analyze ovarian cancer, including identification of the five most frequently mutated genes in COSMIC, as of October 2013, which were *TP53* (65%), *KRAS* (6%), *BRCA1* (4%), *NF1* (4%) and *CHEK2* (3%). Search strategy in COSMIC was: ovary tissue, subtissue (all), cancer histology and serous cancer subhistology. Only serous cancer was included due to its higher frequency and differential frequencies of somatic gene mutations detected in different histologies. Subsequently, PubMed was searched for using the key words specified: ovarian neoplasms [MeSH terms] AND somatic [all fields] AND ("2003/10/18" [PDat]: "2015/02/11" [PDat] AND "humans" [MeSH terms]) and ovarian cancer (MesH terms) AND somatic AND *TP53*, followed by: *P53*; *KRAS*, *BRCA1*, *NF1*, *CHK2* and *CHEK2*. Among 439 unique articles, after exclusions mainly due to absence of individual data for age and mutation, sixteen studies were selected (Table 1).

Selection and exclusion criteria for studies

The following inclusion criteria were used for selection of the publications: (a) studies in which data was available for each individual patient, concerning age and somatic mutation; (b) studies employing whole tumor genome or exome sequencing; (c) studies evaluating mutations in the five candidate genes in tumor specimens using direct sequencing. Exclusion criteria were: (a) studies without individual data; (b) mutation analyzed only through loss of heterozigosity (LOH), Restriction fragment length polymorfism (RFLP), single-strand conformation polymorphism (SSCP) not confirmed by direct sequencing; and (c) other techniques not related with direct sequencing.

References from selected studies, reviews and meta-analysis were checked for other relevant publications. Authors of manuscripts were contacted by email for missing information, most authors replied, but only one was able to report on missing clinical data.[27] Almost all abstracts from studies published in other languages than English were reviewed, but neither one met the inclusion criteria.

TABLE 1 Studies selected in breast and serous ovarian cancer analysis.

Author	Patients (n)	Gene	Methodology
Breast cancer			
Ding et al.[17]	1	All	WGS and/or exome sequencing
Yost et al.[18]	2	All	WGS and/or exome sequencing
Nik-Zainal et al.[19]	21	All	WGS and/or exome sequencing
Banerji et al.[20]	103	All	WGS and/or exome sequencing
Shah et al.[21]	63	All	WGS and/or exome sequencing
Stephens et al.[22]	100	All	WGS and/or exome sequencing
Ellis et al.[23]	317	All	WGS and/or exome sequencing (77 patients), *PIK3CA, TP53, CDHI* and *GATA3* (240 patients)
Jiao et al.[24]	15	All	WGS and/or exome sequencing
Craig et al.[25]	14	All	WGS and/or exome sequencing
Benvenuti et al.[26]	85	*PIK3CA*	Direct sequencing
Miron et al.[27]	80	*PIK3CA*	Direct sequencing
Martins et al.[28]	75	*PIK3CA*	Direct sequencing
Hernandez et al.[29]	13	*PIK3CA*	Sequenom MassArray – direct sequencing
Lima et al.[30]	1	*PTEN*	Direct sequencing
Jong et al.[31]	89	*TP53*	DHPLC – direct sequencing
Lavarino et al.[32]	31	*TP53*	SSCP – direct sequencing
Wistuba et al.[33]	2	*TP53*	SSCP – direct sequencing
Masri et al.[34]	19	*TP53*	Direct sequencing
Lien et al.[35]	14	*TP53*	Direct sequencing
Eachkoti et al.[36]	25	*TP53*	SSCP – direct sequencing
Vincent-Salomon et al.[37]	48	*TP53*	Direct sequencing
Aceto et al.[38]	4	*TP53*	SSCP – direct sequencing
Curtis et al.[39]	820	*TP53*	Direct sequencing
Ripamonti et al.[40]	1	*TP53*	Direct sequencing
Sjoblom et al.[41]	36	*TP53/GATA3/CDHI*	Direct sequencing
Ang et al.[42]	1	*TP53/PIK3CA*	Sequenom MassArray – direct sequencing
Serous ovarian cancer			
Bell et al.[43]	309	All	WGS and/or exome sequencing
Jones et al.[44]	17	All	WGS and/or exome sequencing (8 patients) and direct sequencing (*KRAS* – 9 patients)
Zhang et al.[45]	1	All	WGS and/or exome sequencing
Bashashati et al.[46]	5	All	WGS and/or exome sequencing
Merajver et al.[47]	15	*BRCAI*	SSCP – direct sequencing
Koul et al.[48]	2	*BRCAI*	PTT – SPSS – direct sequencing
Enomoto et al.[49]	10	*KRAS*	Direct sequencing
Fu et al.[50]	10	*KRAS*	Direct sequencing
Mandai et al.[51]	21	*KRAS*	SSCP – direct sequencing
Otsuka et al.[52]	14	*TP53*	SSCP – direct sequencing
Kringen et al.[53]	24	*TP53*	TTGE – direct sequencing
Dehari et al.[54]	6	*TP53/KRAS*	Direct sequencing
Birch et al.[55]	10	*TP53/KRAS*	Direct sequencing
Wojnaeowicz et al.[56]	95	*TP53/KRAS*	Direct sequencing
Sangha et al.[57]	41	*TP53/KRAS/NF1*	PTT – direct sequencing
Kinde et al.[58]	18	*TP53/KRAS/NF1*	Direct sequencing

WGS: whole genome sequencing; DHPLC: denaturing high pressure liquid chromatography; SSCP: single-strand conformation polymorphism.

Data collection

The aim of the present study was to evaluate the rate of somatic mutations in five specific genes, disregarding the type of mutation and the number of mutations in each gene in the same sample. In case of multiple reports of the same data, only one was taken into consideration. Each abstract was reviewed by two investigators independently. In case of any disagreement, the issue was discussed with the group until a consensus was reached.

A Microsoft Excel Database was assembled with included trials and reasons for exclusion of excluded trials. A second datasheet was assembled with the included articles reporting each patient and mutation found: identification of patient, age, tumor histology; histological grade, stage and mutation (presence or absent). Additionally, for breast cancer patients, information about node, ER, PR and HER2, as reported by the authors, was included.

Data analysis

In this work, cut off ages for early age breast cancer and ovarian cancer were 35 and 40 years, respectively. Group ages were then stratified in 7 groups: (1) <30 years, (2) 30-39 years, (3) 40-49 years, (4) 50-59 years, (5) 60-69 years, (6) 70-79 years and (7) ≥80 years. Age groups with less than 10 patients were not taken into consideration for analysis.

Chi-square or Fisher's exact tests were used to evaluate association between variables. Odds ratio (OR) and 95% confidence intervals (95% CIs) were estimated using logistic regression. Correlation between variables was evaluated through Pearson correlation and correlation coefficients (r) are provided. P values ≤ 0.05 were considered significant. The analysis was performed using Statistical Package for the Social Sciences 18.0 (SPSS).

Results

A total of 1980 patients, 5.6% of whom aged less than 36 years, were included in the 26 studies selected (Table 1). In these studies, data available comprehended each patient's age and specific mutations. At first, breast cancer patients were separated in two subsets: younger (≤35 years) *vs*. older (>35 years). Most patients, both younger and older, were diagnosed with invasive ductal cancer (84% in both groups); however, high histological grade (73 *vs*. 46.6%; p<0.001) and ER-negative tumor (45.5 *vs*. 30.6%; p=0.006) as well as node positivity (63.6 *vs*. 45.8%; p=0.044) and advanced disease, clinical stage III/IV (28.8 *vs*. 14.9%; p=0.003), were mainly detected in younger patients.

PIK3CA somatic mutation was more frequently detected in tumors from older patients as compared with younger patients (26.7 *vs*. 6.7%; p=0.014). *TP53* somatic mutation was described in similar frequencies of younger and older patients, 21.6 and 20.1%, respectively.

PTEN, *CDH1* and *GATA3* somatic mutation was investigated only in a small number of younger patients (16 patients each). *PTEN* somatic mutation was detected in 3.3% of all patients and in 1/16 younger patients. *GATA3* and *CDH1* somatic mutations were analyzed in 672 and 564 patients, respectively, and detected in approximately 8% of them, none aged ≤35 years. *CDH1* somatic mutation was detected in almost half (47%) of the lobular cancers and median age of patients was higher in patients harboring *CDH1* somatic mutation than in patients not harboring the mutation (62 *vs*. 57 years; p=0.007, Mann Whitney test).

Each variable significantly associated with age (histological grade, node, clinical stage, estrogen receptor [ER] status) was then tested concomitantly with *PIK3CA* somatic mutation in the subsets of younger and older breast cancer patients, using binary logistic regression. This analysis showed a trend towards a lower chance of ER-positive tumor in younger, as compared with older patients (OR: 0.433; 95% CI: 0.181-1.036; p=0.060); but not for *PIK3CA* somatic mutation (OR: 0.233; 95% CI: 0.029-1.712; p= 0.149).

An association between gene mutations and tumor subtypes was already described; hence, the whole group of patients was then tested for these associations, independent of age. *PIK3CA* somatic mutation was more frequently detected in ER-positive than in ER-negative tumors (28 *vs*. 8%; p<0.001) and *TP53* somatic mutation was more frequently detected in ER-negative (42.8 *vs*. 10.1%; p<0.001) and HER2-positive tumors (27.5 *vs*. 18.6%; p=0.006). Considering the whole group of patients who had both *PIK3CA* and *TP53* analyzed, only 5.5% (35/637) presented both *PIK3CA* and *TP53* somatic mutations, while 49.6% (316/637) presented both *PIK3CA* wild-type (wt) and *TP53* wt.

Following the hypothesis that the number of somatic mutations accumulate along the lifetime,[3] the next step was to evaluate *PIK3CA* and *TP53* somatic mutations according to age groups, classified as <30 years and then every 10 years. Frequency of *PIK3CA* somatic mutation increased in older age groups and reached about 30% in patients aged more than 60 years; *TP53* somatic mutation peaked in 20-30% in patients aged 30-59 years, decreasing thereafter (Figure 1).

ER and HER2 status was also determined according to age groups, as another aim was to evaluate presence of somatic mutations according to tumor characteristics (ER and HER2) in the age groups. Frequency of ER-positive tumors was directly correlated with age and reached

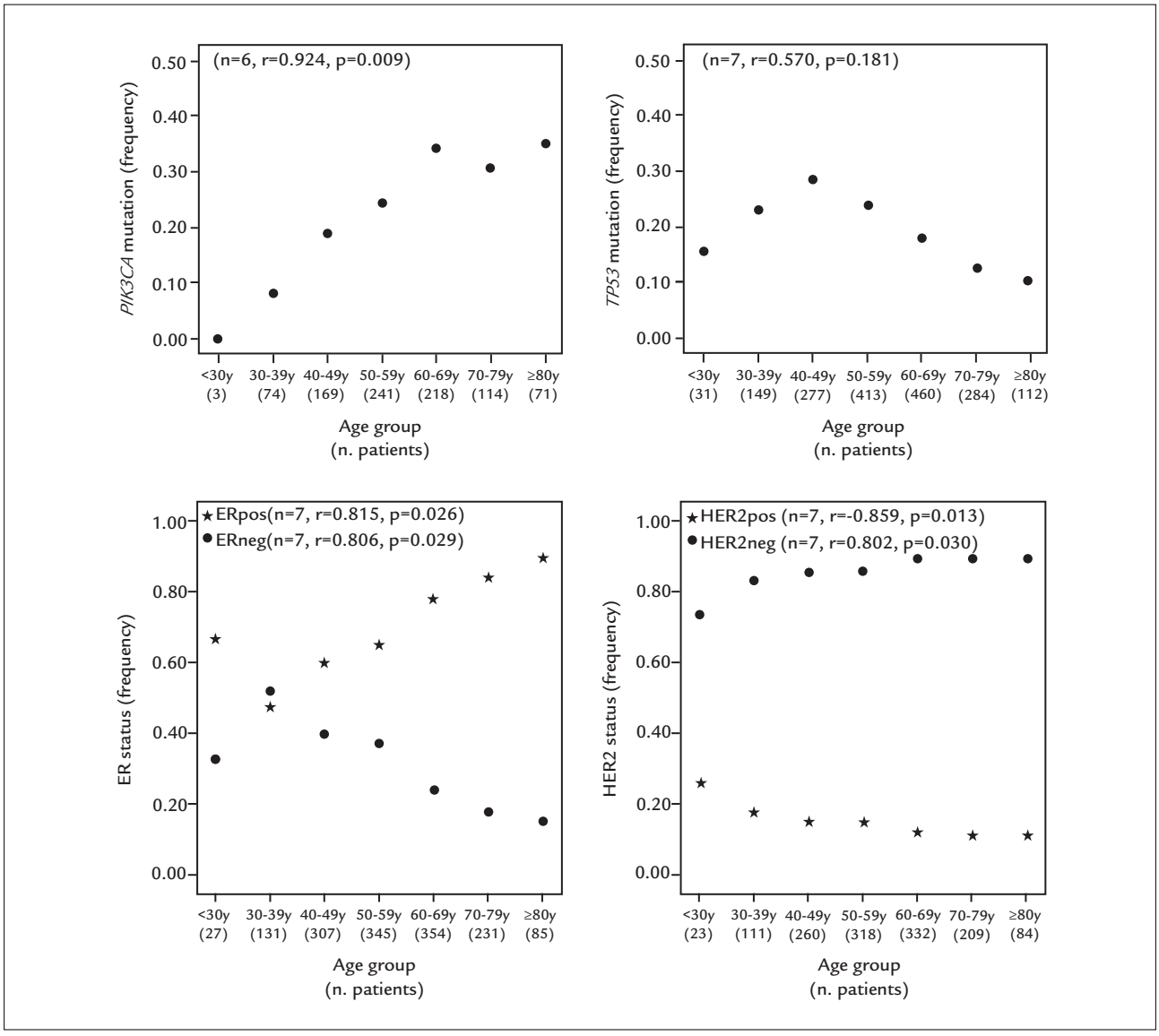

FIGURE 1 Frequency of *PIK3CA* and *TP53* somatic mutation and ER and HER2 expression (positive and negative) according to different age groups (Pearson correlation) (*PIK3CA* n=6, after exclusion of age group < 30 years, as less than 10 patients were available).

80% in women aged 60 years or more. In contrast, frequency of HER2-positive tumors was indirectly correlated with age and maximum level, around 25%, was detected in patients aged less than 30 years (Figure 1).

Afterwards, frequency of *PIK3CA* and *TP53* somatic mutation was evaluated in ER-positive/negative and HER2-positive/negative tumors, according to age groups. There was a trend towards an increased frequency of *PIK3CA* somatic mutation in ER-positive tumors, according to age groups (Figure 2). For patients aged less than 40 years, frequency of *PIK3CA* somatic mutation in ER-positive tumors was low, near 10%. After this age, more than 25% of the ER-positive tumors presented *PIK3CA* somatic mutation. In HER2-negative tumors, a positive correlation in frequency of *PIK3CA* somatic mutation according to age groups was detected. No correlation was observed in frequency of *TP53* mutation according to tumor characteristics and age (Figure 2).

Among 16 studies selected in serous ovarian cancer, 598 samples were evaluated (with 6.8% aged less than 41 years), while other histologies, comprehending 95 samples, were disregarded from further analysis (Table 1). Patients were grouped in younger (≤40 years) and older age (>40 years), the majority of them diagnosed with advanced

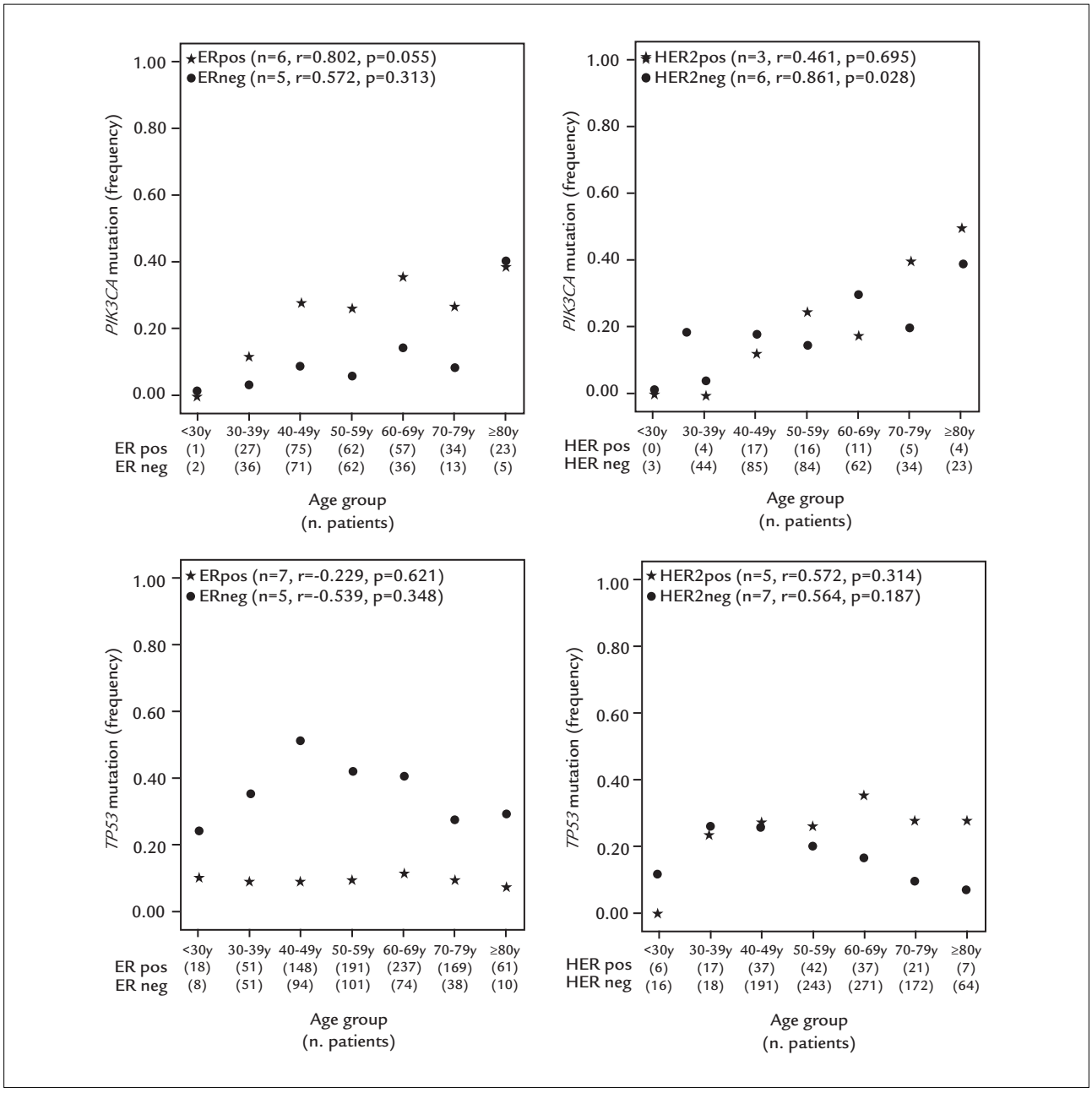

FIGURE 2 Frequency of *PIK3CA* and *TP53* somatic mutation according to expression ER and HER2 (positive and negative) according to different age groups (Pearson correlation). Age groups with less than 10 patients were excluded.

disease (clinical stage III/IV). High grade tumors (histological grade III) were mainly observed in older patients (88.8 *vs.* 65%; p<0.001). *TP53* somatic mutation was rather common, detected in more than 50% of tumors in both age groups, however, more frequently in older patients (86.7 *vs.* 55.2%; p<0.001). *KRAS* somatic mutation was described in less than 3% of the tumors; however, only 35 younger patients were included, among whom, one with mutation. A low frequency of somatic mutation was also observed for *BRCA1* (3.5%), *NF1* (5.5%) and *CHECK2* (0.3%), none detected in younger patients.

Frequency of *TP53* mutation was also tested in age groups, classified as <30 years and then every 10 years, and detected in more than 75% of tumors from patients aged 40 years or more. This evaluation was not performed for the other genes, due to the small number of patients available.

Discussion

We have investigated whether frequency of somatic mutations would differ in younger and older cancer patients. At first, frequency of somatic mutations in *PIK3CA*, *TP53*, *CDH1*, *GATA3* and *PTEN* was evaluated in younger and older breast cancer patients, using a cut off of 35 years. *PIK3CA* somatic mutation was found less frequently in younger (≤ 35 years) than older patients (>35 years) (6.7 *vs.* 26.7%, respectively). In addition, an association between *PIK3CA* somatic mutation and positive expression of ER was detected, as already reported.[59-63] However, in binary logistic regression, only odds ratio (OR) for ER-positive expression (but not for *PIK3CA* somatic mutation) was lower in younger patients.

Analyzing some other manuscripts, that were not included in the present meta-analysis (since individual age of cancer diagnosis was not available), no association between *PIK3CA* somatic mutation and age was found. In these studies, however, a cut point was set at a higher age, 50-55 years or menopause.[62-64] On the other hand, a trend towards association between *PIK3CA* somatic mutation in older patients was also already reported.[65]

PIK3CA somatic mutation frequency was, then, investigated in different age groups (<30 years and then every 10 years) and a direct correlation was verified. Furthermore, a direct correlation of frequency of *PIK3CA* somatic mutation in ER-positive tumors and age groups was detected, indicating that *PIK3CA* somatic mutation frequency increases in aging patients. Hence, it seems likely *PIK3CA* somatic mutation rate increases in ER positive tumors in aging patients.

In the present analysis, *TP53* somatic mutation frequency was similar (around 20%) in both younger and older breast cancer patients. Considering frequency of *TP53* somatic mutation in the age groups, it tended to increase in the early age groups, reaching almost 30% in patients aged 40-49 years, going downwards in older age groups. In agreement, in another manuscript, which was not included in this meta-analysis due to unavailability of age for all patients, but only for *TP53* somatic mutation carriers, *TP53* somatic mutation was reported to be 17% in early onset breast cancer patients (< 37 years).[66] In addition, a fall in *TP53* somatic mutation rate in older age groups, above 59 years, was also reported in a large study.[67] Discrepancies however, evaluating *TP53* somatic mutation frequency and age were also shown, varying from no association[68,69], to reduced[70] or increased age[71] being associated with *TP53* somatic mutation. In the present series, *TP53* somatic mutation was more frequent in ER-negative tumors (41.8%), in accordance with some authors[63,67] but in contrast with others, that found no association.[69,71]

In the current analysis, *PTEN*, *CDH1* and *GATA3* somatic mutation was investigated only in a small number of younger breast cancer patients (16 patients), in whom it seemed to be very infrequent, even absent as in the case of *PTEN* and *CDH1*. In contrast, it is interesting to observe that another recent work reported that *GATA3* somatic mutations tended to occur in tumors from patients aged ≤ 40 years, mainly in luminal-like subtype.[72] In the present analysis, median age of patients presenting *CDH1* somatic mutation was 62 years, in accordance with another study, where mean age was 64.9 years, indicating that it is mainly detected in older patients.[73]

In serous ovarian cancer, *TP53* somatic mutation was rather common and mutation frequency increased with advancing age, in agreement with previous studies.[74-76] In addition, *KRAS* somatic mutation rate was low (<3%), also reflecting data from other authors.[77] *BRCA1* somatic mutation was detected in tumors from 3.5% of the patients, and even though no mutations were detected in younger patients, only 16 were aged less than 41 years. A similarly low *BRCA1* somatic mutation rate was also detected in another study of epithelial ovarian cancer. In that analysis all affected patients presented familial history of breast and/or ovarian cancer and tumor subtype specificity was not reported.[78]

Conclusion

In breast cancer samples, there is a trend towards increasing *PIK3CA* somatic mutation rate in ER-positive tumors in aging patients. *TP53* somatic mutation peaks around 20-30% in patients aged 30-59 years, decreasing thereafter. In addition, *CDH1* somatic mutation seems to be unlikely in younger patients. In ovarian cancer samples *TP53* somatic mutation is rather frequent, detected in more than 50% of tumors in younger and more than 75% of tumors in older patients.

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Resumo

Mutações somáticas em pacientes jovens com câncer de mama e epitelial de ovário: revisão e metanálise

Objetivo: avaliar se mutações somáticas em câncer de mama e seroso de ovário estão associados com pacientes jovens.
Métodos: com base no COSMIC, foram selecionados os cinco genes mais frequentes mutados em câncer de mama e seroso de ovário. Em seguida, realizou-se uma revisão sistemática no PubMed. Pacientes jovens foram classificadas com ≤35 anos e ≤40 anos para câncer de mama e seroso de ovário, respectivamente. Classificaram-se também as pacientes em grupos etários de ≤30 anos, separados a cada 10 anos.
Resultados: vinte e seis (1.980 pacientes, 111 jovens) e 16 estudos (598, 41 jovens) foram selecionados para câncer de mama e seroso de ovário, respectivamente. Em câncer de mama, pacientes jovens apresentaram baixa frequência de mutações somáticas em *PIK3CA*. Tumor HER2 negativo foi associado a mutações somáticas em *PIK3CA* no grupo etário mais avançado, e em tumores ER positivos foi observada uma tendência a essa associação. Mutações somáticas em *TP53* foram observadas em 20% dos tumores, em ambos os grupos (≤35 anos *vs*. ≥35 anos). Mutações somáticas em *PTEN*, *CDH1* e *GATA3* foram analisadas em 16 pacientes e apenas uma apresentou mutação em *PTEN*. Em câncer seroso de ovário, mutações somáticas em *TP53* foram detectadas em mais que 50% dos tumores; entretanto, foram mais frequentes em pacientes idosas.
Conclusão: a frequência de mutações somáticas nos genes selecionados não foi associada com pacientes jovens. Embora muito comum em pacientes com câncer seroso de ovário, mutações somáticas em *TP53* foram mais frequentes em pacientes mais velhas.

Palavras-chave: neoplasias da mama, neoplasias ovarianas, adulto jovem, mutação.

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