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Influence of Age on the Clinical Outcome of Breast Cancer for Men and the Development of Second Primary Cancers

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Abstract

Background.—Low incidence of breast cancer in men (BCM) (<1 % of all breast cancers) has led to a paucity of outcome data. This study evaluated the impact of age on BCM outcomes.

Methods.—For this study, BCM patients treated between 2000 and 2011 were stratified by age (<65 or ≥65 years). Kaplan-Meier methods were used to compare overall survival (OS) and breast cancer-specific survival (BCSS). Competing-risk methods analyzed time to second primary cancers (SPCs), with any-cause death treated as a competing risk.

Results.—The study identified 152 BCM patients with a median age of 64 years (range, 19–96 years). The median body mass index (BMI) was 28 kg/m². Men age 65 years or younger ($n = 78$, 51 %) were more overweight/obese than men older than 65 years ($n = 74$, 49 %) (89 % vs 74 %, respectively; $P = 0.008$). Both groups had similar nodal metastases rates ($P = 0.4$), estrogen receptor positivity ($P = 1$), and human epidermal growth factor receptor 2 (HER2)neu overexpression ($P = 0.6$). Men 65 years of age or younger were more likely to receive chemotherapy ($P = 0.002$). The median follow-up period was 5.8 years (range, 0.1–14.4 years). The 5-year OS was 86 % (95 % confidence interval [CI], 80–93 %), whereas the 5-year BCSS was 95 % (95 % CI, 91–99 %). The BCM patients 65 years of age and younger had better OS ($P = 0.003$) but not BCSS ($P = 0.8$). The 5-year cumulative incidence of SPC was 8.4 % (95 % CI, 3.4–13.4 %). The prior SPC rate was higher for men older than 65 years ($n = 20$, 31 %) than for those age 65 years or younger ($n = 7$, 11 %) ($P = 0.008$). This did not account for differences in life years at risk. No difference was observed in SPC cumulative incidence stratified by age ($P = 0.3$).

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CONFLICTS OF INTEREST Dr. Monica Morrow has received speaking honoraria from Genomic Health.

Conclusions.—Men 65 years of age or younger received more chemotherapy and had improved OS, but not BCSS compared with men older than 65 years. For all BCM, SPC is a risk, and appropriate screening may be warranted.

Breast cancer in men (BCM) accounts for approximately 1 % of all breast cancer cases¹ and less than 1 % of all malignancies in men.² This low incidence has led to a paucity of data with respect to the underlying etiology, management, and outcomes in BCM. There are no randomized trials of BCM, and men are underrepresented in breast cancer research overall.^{3–5} Although BCM more often presents with lymph node involvement, men's stage-matched breast cancer-specific survival (BCSS) is similar to or even more favorable than that of women.^{6–8}

Despite changes in the management of BCM, outcomes have not improved.³ Compared with women, the overall incidence of breast cancer among men is increasing, with an approximate 26 % increase in incidence during the last three decades.⁹

The influence of age on tumor biology, management, and outcomes in women with breast cancer has long been explored.¹⁰ Findings have shown that young age is associated with more aggressive tumor types,¹¹ as well as higher local recurrence (LR) rates and lower survival compared with those for older women.^{12–16} Such data regarding age-related differences in women with breast cancer have led to an evolution in treatment guidelines for older patients.^{17–19} The interplay between age, hormone receptors, and estrogen levels in women make it difficult to apply female age-related differences in tumor biology and outcomes to men.

Second primary cancers (SPCs) after breast cancer in women have been extensively studied.^{20–22} Efforts have been made to investigate this phenomenon in BCM. One early study²³ noted a 2.7 % contralateral breast cancer (CBC) rate and that 10.6 % of men went on to experience the development of an SPC. This resulted in the cause of death in 9 % of all subsequent deaths. Further studies have also reported excess SPC risk after BCM.^{24–26}

This study examined the relationship between age and BCM with respect to presentation, management, and clinical outcomes as well as other clinicopathologic and patient-related factors. The occurrence of SPC may be influenced by age and could have important implications for cancer etiology and preventive screening strategies. This study also investigated the impact of age on the rate and type of non-breast SPC and assessed its effect on survival.

METHODS

After Institutional Review Board approval, we identified all BCM patients who underwent surgical intervention at Memorial Sloan Kettering Cancer Center (MSK) from 1 January 2000 to 31 December 2011. The cohort was divided into two groups according to age at presentation: those 65 years of age or younger versus those older than 65 years.

Clinical, pathologic, and treatment variables were collected and compared between the two groups using Fisher's exact test for categorical variables and the Wilcoxon rank sum test for

continuous variables. Genetic testing information was collected when available. Gynecomastia was determined to be present if noted on mammography or clinical exam. Information about additional SPC was collected before and/or after breast cancer diagnosis. We excluded basal cell and squamous cell carcinoma diagnoses. We noted the history CBC or its subsequent development.

Analyses of overall survival (OS) and BCSS were limited to patients with invasive breast cancer (IBC). We measured OS and BCSS from date of surgery to last follow-up visit or death. The Kaplan-Meier (KM) method estimated OS and BCSS time. The log-rank test was used for between-group comparisons. We examined LRs and distant recurrences (DRs) using a competing-risks approach, in which LR, DR, and death from any cause were treated as competing events. In this study, LR was defined as ipsilateral breast cancer recurrence with or without ipsilateral axillary nodal recurrence or ipsilateral axillary nodal recurrence without ipsilateral breast cancer recurrence. Time to recurrence or death was estimated using cumulative incidence. Gray's test was used for between-group comparisons. Competing-risk methods were used to analyze time to subsequent SPC, with death from any cause treated as a competing event. A *P* value lower than 0.05 was considered statistically significant. All statistical analyses were conducted using R software version 3.4.1 (R Core Development Team, Vienna, Austria) including the “survival” and “cmprsk” packages.

RESULTS

We identified 152 men who underwent surgical intervention at MSK during the study period. The median age at diagnosis was 64 years (range, 19–96 years). A palpable mass or nipple discharge was the chief complaint of 144 patients (95 %). The diagnosis of IBC was determined for 128 men (84 %), whereas 24 men (16 %) had pure ductal carcinoma *in situ* (DCIS). The IBC tumors had a median size of 1.8 cm (range, 0.04–5.3 cm), were estrogen receptor-positive (ER+) in 125 men (82 %), and were overexpressed HER2 in 7 men (5 %).

A family history of breast cancer was recorded for 75 men (49 %). Of the 48 patients who underwent genetic testing, 11 (23 %) carried a mutation (1 *BRCA1*, 10 *BRCA2*). The median body mass index (BMI) for the cohort was 28 kg/m² (range, 19–49 kg/m²), and 71 patients (47 %) in this population had gynecomastia (Table 1).<T1>

Differences in Patient and Tumor Characteristics by Age

The patients were stratified into two groups by age: those 65 years of age or younger (*n* = 78, 51 %) versus those older than 65 years (*n* = 74, 49 %). The median BMI for those 65 years of age or younger was 29 kg/m² (range, 21–49 kg/m²) and significantly higher than the median of 28 kg/m² (range, 19–41 kg/m²) for those older than 65 years (*P* = 0.007). Among those 65 years of age or younger, the proportion with a healthy weight (as indicated by a BMI of 18.5–24.9 kg/m²) was significantly lower than that for those older than 65 years (12 % vs 26 %; *P* = 0.008) (Table 1).

Differences in Breast Cancer Management by Age

The preoperative workup did not differ by age. Surgical management of the breast and the axilla was similar in both age groups. The patients 65 years of age or younger were more

likely to receive chemotherapy (67 %, $n = 43$) than those older than 65 years (38 %, $n = 24$; $P = 0.002$). No difference in endocrine or radiation therapy by age group was observed (Table 2).<T2>

Differences in Recurrence Rates, BCSS, and OS

Outcomes were assessed among the 128 patients with IBC. The median follow-up period among survivors was 5.8 years (range, 0.1–14.4 years) in the IBC cohort. The 5-year OS rate was 86 % (95 % confidence interval [CI], 80–93 %), and the 5-year BCSS rate was 95 % (95 % CI, 91–99 %). The OS was significantly longer for the patients 65 years of age or younger ($P = 0.003$), but there was no difference in BCSS according to age ($P = 0.8$). The LR and DR rates showed no difference by age (Fig. 1).<F1>

SPC

The study identified SPC in 41 men, with 27 men presenting before and 14 after diagnosis (Table 3).<T3> The most common site for SPC after breast cancer was the prostate ($n = 6$). The cumulative incidence of subsequent SPC at 5 years was 8.4 % (95 % CI, 3.4–13.4 %) (Fig. 2A).<F2> A history of CBC was noted for two men (1.3 %), and subsequent CBC developed in three men. The patients were stratified by age 65 years or younger ($n = 64$, 50 %) versus age older than 65 years ($n = 64$, 50 %). The rate of prior SPC was significantly higher for the patients older than 65 years ($n = 20$, 31 %) than for those age 65 years or younger ($n = 7$, 11 %) ($P = 0.008$), although this analysis did not account for the difference in life years at risk. The cumulative incidence of all SPCs after the diagnosis of breast cancer did not differ by age group ($P = 0.3$) (Fig. 2B).

DISCUSSION

The interplay between age and breast cancer in women has been extensively researched. Age-related hormonal factors and variable genetic mutations in women with breast cancer make it difficult to extrapolate age-related influences among women to those seen in men. The current study aimed to examine the relationship between age and the presentation, management, and clinical outcomes of BCM. In this study population, the median age at presentation was 64 years, similar to that in other published BCM studies.^{27–29}

An international collaborative study between the European Organization for Research and Treatment of Cancer (EORTC), the Translational Breast Cancer Research Consortium (TBCRC), the North American Breast Cancer Group (NABCG), and the Breast International Group (BIG) recently published a characterization of BCM using a cohort of 1483 pooled cases.³⁰ Their median age was 68.4 years. The younger median age at presentation in our study likely reflects patterns of referral to a tertiary specialized cancer center, but still is older than the median age at presentation (62 years) among women demonstrated in the Surveillance, Epidemiology, and End Results (SEER) database.³¹

Our population included IBC (84 %) and DCIS (16 %), and the pathologic subtypes did not differ with age. Frequently, DCIS has been excluded in the published series of BCM.^{27,30} La Verde et al.²⁹ reported a DCIS rate of 6 % in their series, but the pathologic subtype was not defined for 27 % of their population. Previously reported SEER data also reported T0/T1

tumors but did not give any further breakdown of DCIS-only cases.³² We had predominantly early BCM, with 97 % of the patients having T1 or T2 tumors. Only four patients presented with T3 or T4 tumors, and they all were older than 65 years. Our nodal stage, tumor grade, and ER/progesterone receptor (PR) status were similar to those of previously published series^{27,29,30} and did not differ by age.

Men 65 years of age or younger had a significantly better OS than those older than 65 years. The same age-related difference was not seen in BCSS. This was similarly demonstrated in the EORTC 10085 study, with clear separation of the Kaplan-Meier OS curves for those 66 to 75 years of age and those older than 75 years from those 65 years or age or younger, whereas the Kaplan-Meier curves for breast cancer mortality by age demonstrated no differences.³⁰ Leone et al.³² performed multivariate analysis for OS and found a hazard ratio of 2.97 (95 % CI, 2.06–4.27; $P < 0.0001$) between men older than 50 years and those older than 64 years.

The relationship between obesity and BCM has been previously established.^{33–38} Brinton et al.³⁸ reported results of an analysis based on individual participant data from 11 case-control studies and 10 cohort studies comprising 2405 BCM and 52013 male controls. Based on these data, the odds ratio (OR) for BCM associated with adult BMI at presentation (healthy weight [BMI, 18.5–24.9 kg/m²] vs obesity [BMI, ≥ 30 kg/m²]) was 1.35 (95 % CI, 1.12–1.62). Our study found that the mean BMI was higher in our younger cohort (age ≤ 65 years) and that the proportion of those 65 years or younger at a healthy weight (BMI, 18.5–24.9 kg/m²) was significantly lower than that of those older than 65 years. Brinton et al.³⁸ stratified their population by age using a median age of 66 years and observed BMI as a risk factor for BCM.

The strongest effect of BMI (highest vs lowest tertile) seemed to be among those younger than 66 years (OR, 1.44; 95 % CI, 1.17–1.76; $P < 0.001$ rather than among those 66 years of age or older (1.17; 95 % CI, 0.94–1.45; $P = 0.15$).³⁸ Studies have shown obesity to be associated with an increased risk of breast cancer in women, and the risk is thought to be due in part to the peripheral conversion of androgens to estrogens.^{32–34} In men, obesity is associated with high estrogen levels as well as low testosterone and sex hormone-binding globulin levels,^{39,40} leading to greater estrogen bioavailability.

In most cases, BCM is hormone sensitive. In our study group 82 % of the cancers were ER-positive, with 80 % of the men with IBC prescribed adjuvant endocrine therapy. This was similar to the use of endocrine therapy reported from the EORTC 10085/TBCRC/BIG/NABCG international study (76.8 %).³⁰ We did not find that the use of endocrine therapy differed between those 65 years of age or younger and those older than 65 years.

The use of adjuvant chemotherapy in our study (52 %) was much higher than in the EORTC 10085 study (29.8 %).³⁰ This may be a reflection of differing practice and selection bias in a tertiary referral cancer center. We did find a significant difference in receipt of chemotherapy between the two age cohorts (67 % of those ≤ 65 years of age with IBC received chemotherapy vs only 38 % of those >65 years of age). This likely was due to the associated

comorbidities of increasing age, patient performance status, and suitability for cytotoxic chemotherapy.

Due to the high rate of hormone sensitivity in BCM, most patients would have the option of endocrine therapy, which has fewer side effects. A recent study of Oncotype DX (Genomic Health, Redwood City, CA, USA) in BCM demonstrated differences in recurrence score (RS) distributions compared with breast cancer. The study showed that women with breast cancer had a greater proportion of higher RS (>31). However, and similar to women with lower RS results, men had low mortality from ER-positive breast cancer and should be spared the risks associated with overtreatment, particularly chemotherapy.⁴¹ Oncotype DX testing was used in the later years of our cohort but was available only for 13 patients. Therefore, most decisions about adjuvant chemotherapy were made without RS data. This was a limitation our study.

Published reports to date on SPC incidence and organ site after BCM have varied. Auvinen et al.²⁶ found that overall SPC risk was not increased (standardized incidence ratio [SIR], 0.99; 95 % CI, 0.86–1.13) in a cohort of 1788 men from the SEER database during the period 1973 to 1996. However, other investigators have reported an increased risk of SPC. A Taiwan national survey of 578 BCM cases recently reported a significantly higher observed risk for SPC (SIR, 2.17; 95 % CI, 1.70–2.73) after a median follow-up period of 3.85 years.⁴² Additionally, data from 1926 BCM cases recruited from the California Cancer Registry from 1988 to 2003 also demonstrated a significantly higher risk of second cancer (SIR, 1.16; 95 % CI, 1.01–1.32).²⁵ Of 3409 BCM patients pooled from 13 cancer registries, 12.5 % experienced an SPC, with an overall excess risk of 34 %.²⁴

In our study, we found a cumulative incidence of non-breast SPC of 8.4 % at 5 years. The prostate was the most common SPC organ site. For 6 patients, prostate cancer developed after their diagnosis of breast cancer, and 10 patients (7.8 %) in our cohort of 128 had a prior diagnosis of an SPC.

The possible link between prostate cancer and BCM has been previously reported.^{43–45} Current theories for breast and prostate cancer development incorporate hormonal, dietary, genetic, and other factors.⁴⁶ Hemminki et al.,²⁴ in the largest published series of BCM, also found an increased risk of prostate cancer (SIR, 1.61; 95 % CI, 1.34–1.93). This finding is supported by other series.^{23,47} We stratified our population by age (≤ 65 and >65 years) and did not find any difference in the cumulative incidence of SPC. Satram-Hoang et al.²⁵ stratified their population to assess for an age effect for SPC risk (<60 , 60–69, and 70 years). They found the highest SIRs for SPC in the youngest population, and the risk decreased with increasing age. This was true for the populations including and excluding CBCs. This finding is not surprising because an increased cancer risk would be expected among the youngest men with the longest life expectancy and increased lead time to further cancer development. Our population may have been too small for examination of this difference, and our median follow-up period of years may have been too short for detection of this effect. We did find a significantly higher rate of prior SPC among the men older than 65 years (31 %) than among those 65 years of age or younger (11 %; $P=0.008$), likely due to a lead time effect in the older cohort.

CONCLUSIONS

Given the lack of prospective randomized studies and the limited involvement of men in clinical trials, much of what we know of BCM has resulted from retrospective analyses of similar data sets. Until then, <AQ2> physicians managing BCM should strive to treat their patients according to the standards of the best evidence currently available. The relationship between obesity and younger age at diagnosis needs further study given the worldwide epidemic of growing obesity rates. Men with breast cancer have a risk for SPCs, particularly those with prostate cancer. Appropriate screening should be considered. Genetic counseling and testing should continue to be offered to all men with breast cancer.

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SYNOPSIS

This study evaluated the impact of age on male breast cancer outcomes and found that men age 65 years or younger received more chemotherapy and had improved overall survival but not breast cancer-specific survival compared with men older than 65 years.

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FIG. 1.

Cumulative incidence curves comparing (A) local recurrence and (B) distant recurrence by age, and Kaplan-Meier curves comparing (C) breast cancer-specific survival and (D) overall survival by age.

FIG. 2.

A Competing-risk curves of second primary cancer development, with death as a competing risk. **B** Cumulative incidence of secondary primary cancer after male breast cancer diagnosis stratified by age ≤ 65 and > 65 years. *Boxed* and *unboxed* labels represent cumulative incidence of death and second primary cancer rates, respectively, at 5 and 10 years.

TABLE 1

Age and clinicopathologic characteristics: entire male breast cancer cohort

	Total (n= 152) n (%)	Age ≤65 years (n= 78) n (%)	Age >65 years (n = 74) n (%)	P Value
Median age: years (range)	64 (19–96)	54 (19–65)	74 (65–96)	NA
BMI category (kg/m ²)				0.008
Normal (18.5–25)	28 (18)	9 (12)	19 (26)	
Overweight (>25–30)	70 (46)	35 (45)	35 (47)	
Obese (>30–40)	43 (28)	24 (31)	19 (26)	
Severely obese (>40)	11 (7)	10 (13)	1 (1)	
Period				0.9
2001–2004	49 (32)	26 (33)	23 (31)	
2005–2008	53 (35)	26 (33)	27 (37)	
2009–2011	50 (33)	26 (33)	24 (32)	
Family history				0.4
Yes	75 (49)	41 (53)	34 (46)	
No	76 (50)	36 (46)	40 (54)	
Unknown	1 (1)	1 (1)	0 (0)	
Gynecomastia				0.3
Yes	71 (47)	40 (51)	31 (42)	
No	16 (11)	6 (8)	10 (14)	
Unknown	65 (43)	32 (41)	33 (45)	
Presentation				0.5
Physical findings	144 (95)	73 (94)	71 (96)	
Mammography	3 (2)	1 (1)	2 (3)	
Incidental	5 (3)	4 (5)	1 (1)	
Median tumor size: mm (range)	18 (0.4–53)	20 (0.4–38)	17 (1–53)	0.5
Tumor type				0.5
IBC	128 (84)	64 (82)	64 (87)	
DCIS	24 (16)	14 (18)	10 (14)	
T stage				0.08
Tis, T1, T1mic	97 (64)	47 (60)	50 (68)	
T2	50 (33)	30 (39)	20 (27)	
T3	2 (1)	0 (0)	2 (3)	
T4	2 (1)	0 (0)	2 (3)	
TX	1 (1)	1 (1)	0 (0)	
N stage				0.4
N0/1	124 (82)	63 (81)	61 (82)	
N2	14 (9)	10 (13)	4 (5)	
N3	7 (5)	3 (4)	4 (5)	
NX	7 (5)	2 (3)	5 (7)	
Nuclear grade				0.2

	Total (n= 152) n (%)	Age ≤ 65 years (n= 78) n (%)	Age >65 years (n = 74) n (%)	P Value
Low	11 (7)	8 (10)	3 (4)	
Intermediate	79 (52)	37 (47)	42 (57)	
High	38 (25)	22 (28)	16 (22)	
NA	24 (16)	11 (14)	13 (18)	
Multicentric/focal				1
Yes	10 (7)	5 (6)	5 (7)	1
No	142 (93)	73 (94)	69 (93)	
ER				
Positive	125 (82)	62 (80)	63 (85)	
Negative	3 (2)	2 (3)	1 (1)	0.5
Not performed	24 (16)	14 (18)	10 (14)	
PR				
Positive	106 (70)	51 (65)	55 (74)	0.6
Negative	21 (14)	12 (15)	9 (12)	
Not performed	25 (16)	15 (19)	10 (14)	
HER2				0.6
Positive	7 (5)	3 (4)	4 (5)	
Negative	116 (76)	60 (77)	56 (76)	
Not done	29 (19)	15 (19)	14 (19)	0.6
Nipple involvement				
Yes	47 (31)	26 (33)	21 (28)	
No	104 (68)	52 (67)	52 (70)	0.3
Unknown	1 (1)	0 (0)	1 (1)	
Margin status				
Negative	144 (95)	75 (96)	69 (93)	
Positive/close	7 (5)	2 (3)	5 (7)	
Unknown	1 (1)	1 (1)	0 (0)	

NA, not applicable; BMI, body mass index; IBC, invasive breast cancer; DCIS, ductal carcinoma *in situ*; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2

TABLE 2

Preoperative, operative, and adjuvant management of entire male breast cancer cohort stratified by age

	Total (n = 152) n (%)	Age ≤ 65 years (n = 78) n (%)	Age > 65 years (n = 74) n (%)	P Value
Mammogram				0.3
Abnormal	109(72)	55 (71)	54 (73)	
Normal	12(8)	8(10)	4(5)	
Not performed	31(20)	15(19)	16(22)	
Ultrasound				1
Abnormal	83 (55)	41 (53)	42 (57)	
Normal	8(5)	4(5)	4(5)	
Not performed	61 (40)	33(42)	28 (38)	
MRI				1
Performed	3(2)	2(3)	1(1)	
Biopsy				0.8
Core	60 (40)	30 (39)	30(41)	
Excision	65 (43)	35 (45)	30(41)	
FNA	26(17)	12(15)	14(19)	
Not performed	1(1)	1(1)	0(0)	
Breast surgery				0.5
Lumpectomy	8(5)	3(4)	5(7)	
Mastectomy	144 (95)	75(96)	69 (93)	
Axillary surgery				1
SLNB alone	81 (53)	41 (53)	40(54)	
SLNB and ALND	53 (35)	28 (36)	25 (34)	
ALND alone	7(5)	4(5)	3(4)	
No axillary surgery	11(7)	5(6)	6(8)	
Chemotherapy ^a				0.002
Yes	67 (52)	43 (67)	24 (38)	
No	55(43)	19 (30)	36 (56)	
Unknown	6(5)	2(3)	4(6)	
Endocrine				0.9
Yes	105 (69)	52 (67)	53 (72)	
No	38 (25)	20 (26)	18 (24)	
Unknown	9(6)	6(8)	3(4)	
Radiotherapy				0.8
Yes	24(16)	13(17)	11(15)	
No	121 (80)	61 (78)	60(81)	
Unknown	7(5)	4(5)	3(4)	

MRI, magnetic resonance imaging; FNA, fine-needle aspiration; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection

^aInvasive breast cancers only

TABLE 3

Breakdown of Organ Site of Prior and Subsequent Second Primary Cancers in the Entire Population of Male Breast Cancers (n=128)

	Total SPC (n=41) n	SPC before BCM (n = 27) n (%)	SPC after BCM (n = 14) n
Prostate	16	10(7.8)	6
Bladder	6	4(3.1)	2
Melanoma	5	4(3.1)	1
Esophageal	3	1 (0.8)	2
Hodgkin's lymphoma	2	2(1.6)	0
Lung	1	0	1
Renal	2	1 (0.8)	1
Acute myeloid leukemia	1	0	1
Other	5	5 (3.9)	-
Breast	5	2(1.6)	3

SPC, second primary cancer; BCM, breast cancer in men

AQ1: "rather than among those 66 years of age or older (1.17; 95 % CI, 0.94–1.45; $P=0.15$)" correct?

AQ2: "Until then"? Until when? Please clarify.

AQ3: Please update ref 30 with vol and pg nos.

AQ4: Please provide access date in ref 31.