RESEARCH ARTICLE

Breast Cancer in Tunisia: Association of Body Mass Index with Histopathological Aspects of Tumors

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Abstract

Background: Previous studies have suggested a link between obesity and breast cancer (BC). However, there is no universal consensus, especially in population based studies. Because only few studies have been conducted on African women, we aimed here to assess the relationship between BMI at time of diagnosis and the BC histopathological features among Tunisian patients according to menopausal status using a hospital-based prospective cohort study. Materials and Methods: Clinical and pathological data were collected from 262 patients stratified on four groups according to their BMI. The relationship between BMI and histopathological features at diagnosis was analysed using univariate and multivariate analysis. Receiver-operating characteristic (ROC) curves were used to evaluate the performance of BMI in predicting of high tumor grade, in comparison to ki-67 index of proliferation. Results: Obesity was correlated with larger tumors, advanced grade and with ER-PR-Her2+ BC subtype. An association of BMI with tumor size and tumor grade was observed in both premenopausal and postmenopausal women. Additionally, a significant association between BMI and ER+, ER+PR+Her2+ and ER-PR-Her2+ status was revealed for premenopausal patients, while only ER+PR+Her2+ was associated with BMI for postmenopausal women. Finally, our results showed that compared to Ki67 proliferation index, BMI is a useful prognostic marker of high grade BC tumors. Conclusions: These data are the first to show that in Tunisia obese women suffering from BC have significantly larger tumors and advanced tumor grade and that higher BMI might influence tumor characteristics and behavior.

Keywords: Breast cancer - obesity - body mass index - tumor size - Tunisia

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Introduction

Breast cancer (BC) is the first female malignancy with 1,38 millions of annual cases worldwide in 2008 and an incidence varying from 18 in Subsaharian Africa to >90/100000 in occidental countries (Ferlay et al., 2010). In Tunisia, BC represents 25-30% of all female malignancies, with 2000 annual cases and with an incidence at 30/100000 that doubled during the last 20 years (Missaoui et al., 2011; 2012). Although BC is thought to be a frequent cancer in the developed countries, a majority of all BC deaths occurs in developing world. Infect, increased urbanization and adoption of western lifestyles have augmented BC rates in the developing countries.

The etiology of BC is not well defined. Several risk factors may be involved on the development of this pathology such as genetic, hormonal, environmental, sociobiological and physiological factors. Many of these risk factors are not reversible, but some, such as obesity, could be modified. Numerous observational studies have investigated the association between obesity and BC (De Pergola and Silvestris, 2013; Minicozzi et al., 2013; Ronco et al., 2012; Sangrajrang et al., 2013 ; Renehan et al., 2008; Majeed et al., 2014; Xing et al., 2014). However, there is no universal consensus on the relationship between BMI and BC, especially in population-based studies. The majority of studies indicating an impact of obesity on BC development have been conducted in Western countries. In our knowledge, so far, only four studies among African women living in Africa have been conducted to estimate a summary measure of the effect of BMI on BC risk (one in Tunisia (Labidi et al., 2008) and three in Nigeria (Adebamowo et al., 2003; Okobia et al., 2006; Ogundiran et al., 2012). Yet, none of these studies have estimated the impact of obesity at diagnostic on histopathological characteristic of BC. In the present study, therefore, we investigate the relationship between BMI and the prognostic markers of BC among Tunisian

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patients according to menopausal status using a hospital-based retrospective cohort study.

Materials and Methods

Patients

This study was conducted in the department of pathology at Department of Medical Oncology, Abderrahman Mami Hospital, Tunis, Tunisia and performed in 262 BC patients. The BC patients were included according to the following criteria: women who (1) had a new histologically confirmed diagnosis of BC; (2) were not treated with radiotherapy, chemotherapy, or anti-estrogens during the previous 6 months; and (3) were not pregnant. The study was approved by the local ethic committee. The ER, PR and HER2 status was centrally reviewed in the pathology department. The histological grade was determined according to the criteria reported by Bloom and Richardson and the tumor size and nodal status were assessed pathologically from surgical specimens. Staining for Ki-67 was performed in the Dako Autostainer Plus automated slide processing system (Dako) with a 1:100 dilution of the monoclonal mouse anti-human Ki67 antibody, clone MIB-1 (DAKO, Glostrup, Denmark). Staining was evaluated by an experienced pathologist without prior knowledge of patient outcome or tumor characteristics The proliferation KI-67 index is considered low or negative, when there are 25% or less stained nuclei and it is considered positive or high, when there are more than 25% of stained nuclei.

Statistical analysis

For the statistical analysis, patients were evaluated according to BMI. Patients with BMI <25 kg/m^2 were classified as normal weight. Those with BMI between 25 and 29.9 kg/m^2 were classified as overweight, those with BMI between 30 and 34.9 kg/m^2 were classified as obese and those with BMI≥35 were classified as severe obese. In this study, the data were analyzed using SPSS software (version 20; SPSS Inc., Chicago, IL, USA). A two-sided p value of <0.05 was considered as statistically significant.

Receiver-operating characteristic (ROC) curves were constructed, and the area under the curve (AUC) was calculated to evaluate the performance of BMI as a predictor of tumor grading. An AUC of 1.0 represents error-free prediction of cancer status in all samples, whereas an AUC of 0.50 represents a fifty percent likelihood of a correct prediction of cancer status. The larger the AUC-ROC, the greater is the discriminatory power of the BMI for the outcome.

Results

The demographic characteristics of breast-cancer patients

The mean age of BC patients was 50.9 (±11.9) for the entire population. The family history of BC was positive in 85 (33.7%) patients. Patients were divided into four groups based on their BMI; normal weight group consisted of 62 (23.6%) patients, overweight group consisted of 103 (39.3%), 71 (27%) women were in obese group and 26 (9.9%) were in severe obese group. Obese women tended to be older at diagnosis of BC (χ^2=0.097, p=0.026) and accounted for a greater percentage of post-menopausal women (60.8%) than pre-menopausal women (39.2%) (p=0.025). No significant difference in rates of BC family history was seen between the four BMI groups.

Association of BMI with clinicopathologic variables

We examined the association of the categorical BMI with the clinicopathologic variables at the time of diagnosis. Higher BMI was significantly associated with tumor size (p=0.000) and with more advanced grade tumors at diagnosis (p=0.002). Patients had mean baseline BMI of 27.65 kg/m^2 when presenting with stage I disease, 27.8 kg/m^2 with stage II, and 30.011 kg/m^2 with stage III disease. This corresponded to 30/73 (41.09%) of patients with baseline 30≤BMI<35 kg/m^2 having stage III at presentation and 15/26 (57.6%) with baseline BMI ≥ 35 kg/m^2 compared with only 46/159 (28.9%) of patients with BMI <30 kg/m^2 (p=0.025). Among all cases, statistically no significant differences were found in the distribution of pathological characteristics including, ER, PR and Her2 status alone in the BMI groups. Nevertheless, a significant association of BMI with combined ER-PR-HER2+ BC tumors was found (p=0.021). Finally, a signification association of Ki-67 index with BMI was observed (p=0.027). These results are shown in (Table 1).

Association of tumor features with BMI according to menopausal status

The correlations between BMI and tumor features were evaluated in pre-menopausal and post-menopausal groups (Table 2). Tumor size and grade were correlated with BMI in both groups (p=0.000 and p=0.049 respectively for pre-menopausal patients; p=0.000 and p=0.011 respectively for post-menopausal patients). HER-2 and PR were not associated with obesity either in premenopausal or postmenopausal patients. However, ER status has greater relation with obesity in premenopausal cases (p=0.004). Additionally, among the pre-menopausal cases, we observe a statistically significant association between BMI and the combined ER+PR+Her2+ and ER- PR-Her2+ status (p=0.008 and p=0.049 respectively). While, only the combined status ER+PR+Her2+ was significantly associated with BMI in post-menopausal women.

Diagnostic performance of BMI for predicting high BC tumor grade

We performed ROC curves in order to evaluate the pertinence of the use of BMI as a marker of high tumor grade. The diagnostic capacity of BMI for detection of grade III tumors was compared to the performance of Ki-67 index. As it is shown in Figure 1, the area under curve (AUC) for BMI was 0.66±0.043 and for Ki-67 was 0.639±0.046. A cut-off value of 28.67 kg/m^2 for BMI predicted presence of grade III BC with 61.3% sensitivity and 63% specificity. Interestingly, The AUC increases when we consider only BC patients under 40 years of age (AUC= 0.73±0.09). Finally, the discriminative power of BMI was investigated on BC subtypes according to the menopausal status. These findings are shown in Table 3. Altogether, these results indicate that BMI is useful as a

Table 1. Association of BMI with Clinicopathologic Variables

		BMI< 25	25≤ BMI< 30	30≤ BMI< 35	BMI≥35	P value
Tumor size	< 2cm	42 (67.7%)	29 (28.1%)	8 (11.2%)	2 (7.6%)	0
	2-5cm	18 (29%)	55 (53.4%)	49 (69%)	16 (61.5%)	
	> 5cm	0 (0%)	13 (12.6%)	14 (19.7%)	8 (30.7%)	
	Unknown	2 (3.22%)	6 (5.8%)	0 (0%)	0 (0%)	
Tumor grade	Grade I	6 (9.6%)	11 (10.5%)	8 (10.9%)	0 (0%)	0
	Grade II	38 (61.2%)	58 (55.7%)	35 (47.9%)	11 (42.3%)	
	Grade III	15 (24.1%)	31 (29.8%)	30 (41.09%)	15 (57.6%)	
	Unknown	3 (4.8%)	3 (2.8%)	0 (0%)	0 (0%)	
Lymph node metasis	No	48 (81.3%)	83 (79.8%)	55 (75.3%)	19 (73%)	0.12
	Yes	5 (8.4%)	10 (9.6%)	9 (12.3%)	5 (19.2%)	
	Unkown	6 (10.1%)	11 (10.5%)	9 (12.3%)	2 (7.6%)	
Expression of tumor marker						
ER status	Positive	39 (66.1%)	62 (59.6%)	42 (57.5%)	13 (50%)	0.05
	Negative	15 (25.4%)	35 (33.6%)	26 (35.7%)	12 (46.1%)	
	Unknown	5 (8.4%)	7 (6.7%)	5 (6.8%)	1 (3.8%)	
PR status	Positive	34 (57.62%)	57 (54.8%)	38 (52%)	13 (50%)	0.27
	Negative	21 (35.5%)	38 (36.5%)	28 (38.3%)	12 (46.1%)	
	Unknown	4 (6.7%)	9 (8.6%)	(9.58%)	1 (3.8%)	
Her2 status	Positive	30 (50.8%)	55 (52.8%)	42 (57.5%)	17 (65.3%)	0.33
	Negative	22 (37.2%)	44 (42.3%)	27 (36.9%)	8 (30.7%)	
	Unknown	7 (11.8%)	5 (4.8%)	4 (5.4%)	1 (3.8%)	
ER/PR satus	ER+/PR+	34 (24.5%)	55 (39.5%)	38 (27.5%)	12 (8.6%)	0.18
	ER+/PR-	5 (35.7%)	5 (35.7%)	3 (21.4%)	1 (7.1%)	0.24
	ER-/PR+	0 (0%)	2 (66.7%)	0 (0%)	1 (33.3%)	0.43
	ER-/PR-	15 (17.9%)	33 (39.3%)	25 (29.8%)	11 (13.1%)	0.08
ER/PR/Her2 status	ER+/Her2-	18 (29.5%)	20 (32.8%)	17 (27.9%)	6 (9.8%)	0.37
	PR+/Her2-	15 (26.8%)	19 (33.9%)	17 (30.4%)	5 (8.9%)	0.5
	ER+/Her2+	20 (21.7%)	41 (44.6%)	24 (26.1%)	7 (7.6%)	0.36
	PR+/Her2+	18 (21.4%)	37 (44%)	21 (25%)	8 (9%)	0.77
	ER+/PR+/Her2-	15 (25.4%)	17 (16.3%)	17 (23.2%)	5 (19.2%)	0.47
	ER+/PR+/Her2+	18 (30.5%)	37 (35.5%)	21 (28.7%)	7 (26.9%)	0.51
	ER-/PR-/Her2+	9 (15.2%)	13 (12.5%)	17 (23.2%)	9 (34.6%)	0.02
	ER-PR-Her2-	4 (6.7%)	19 (18.2%)	8 (10.9%)	2 (7.6%)	0.97
Ki-67 Proliferation Index	Low	22 (37.2)	36 (34.6%)	21 (25.3%)	4 (4.8%)	0.02
	High	12 (20.3%)	39 (37.5%)	16 (21.9%)	12 (46.1%)	
	Unknown	25 (42.3%)	29 (27.8%)	36 (49.3%)	10 (38.4%)	

Table 2. Tumor Features Correlation with BMI according to the Menopausal Status

	Premenopausal (N= 121)					Postmenauposal (N= 141)				
	BMI<25	25≤BMI<30	30≤BMI<35	BMI≥35	p value	BMI<25	25≤BMI<30	30≤BMI<35	BMI≥35	p value
Patients (%)	36 (29.8%)	47 (38.8%)	27 (22.3%)	11 (9.1%)		23 (16.3%)	57 (40.4%)	46 (32.6%)	15 (10.6%)	
Tumor size										
<2cm	23 (63.8%)	13 (27.6%)	4 (14.8%)	0 (0%)	0.00	17 (73.91%)	18 (31.5%)	3 (6.5%)	2 (13.3%)	0.000
2-5cm	13 (36.1%)	21 (44.6%)	13 (48.1%)	4 (36.3%)		4 (17.3%)	30 (52.6%)	34 (73.9%)	8 (53.3%)	
>5cm	0 (0%)	10 (21.2%)	9 (33.3%)	7 (63.6%)		0	6 (10.5%)	9 (19.5%)	5 (33.3%)	
Unknown	0 (0%)	0 (0%)	1 (3.7%)	0 (0%)		2 (8.6%)	3 (5.2%)	0 (0%)	0 (0%)	
Tumor grade										
Grade I	4 (11.1%)	3 (6.3%)	5 (18.5%)	0 (0%)	0.04	2 (8.6%)	8 (14.0%)	3 (6.5%)	0 (0%)	0.01
Grade II	21 (58.3%)	31 (65.9%)	12 (44.4%)	4 (36.3%)		17 (73.9%)	27 (47.3%)	23 (50%)	7 (46.6%)	
Grade III	11 (30.5)	12 (25.5%)	10 (37%)	7 (63.6%)		4 (17.3%)	19 (33.3%)	20 (43.4%)	8 (53.3%)	
Unknown	0 (0%)	0 (0%)	0 (0%)	0 (0%)		0 (0%)	3 (5.2%)	0 (0%)	0 (0%)	
Lymph node metasis										
No	30 (83.3%)	38 (80.85%)	21 (77.77%)	9 (81.81%)	0.61	18 (78.2%)	45 (78.9%)	34 (73.9%)	10 (66.6%)	0.1
Yes	2 (5.55%)	6 (12.7%)	2 (7.4%)	1 (9%)		3 (13%)	4 (7%)	7 (15.2%)	4 (26.6%)	
Unkown	4 (11.11%)	3 (6.38%)	4 (14.8%)	1 (9%)		2 (8.6%)	8 (14%)	5 (10.8%)	1 (6.6%)	
ER status										
Positive	28 (77.7%)	33 (70.2%)	16 (59.2%)	5 (45.4%)	0.004	11 (47.8%)	29 (50.8%)	26 (56.5%)	8 (53.3%)	0.68
Negative	5 (13.8%)	11 (23.4%)	7 (25.9%)	6 (54.5%)		10 (43.4%)	24 (42.1%)	19 (41.3%)	6 (40%)	
Unknown	3 (8.3%)	3 (6.3%)	4 (14.8%)	0 (0%)		2 (8.6%)	4 (7%)	1 (2.1%)	1 (6.6%)	
PR status										
Positive	26 (72.2%)	33 (70.2%)	15 (55.5%)	5 (45.4%)	0.05	8 (34.7%)	24 (42.1%)	23 (50%)	8 (53.3%)	0.21
Negative	8 (22.2%)	11 (23.4%)	7 (25.9%)	6 (54.5%)		13 (56.5%)	27 (47.3%)	21 (45.6%)	6 (40%)	
Unknown	2 (5.55%)	3 (6.3%)	5 (18.5%)	0 (0%)		2 (8.6%)	6 (10.5%)	2 (4.3%)	1 (6.66%)	
Her2 status										
Positive	20 (55.5%)	28 (59.5%)	14 (51.8%)	8 (72.7%)	0.69	10 (43.4%)	27 (47.3%)	28 (60.8%)	9 (60%)	0.23
Negative	13 (36.1%)	18 (38.2%)	11 (40.7%)	3 (27.2%)		9 (39.1%)	26 (45.6%)	16 (34.7%)	5 (33.3%)	
Unknown	3 (8.33%)	1 (2.1%)	2 (7.4%)	0 (0%)		4 (17.3%)	4 (7%)	2 (4.3%)	1 (6.66%)	
Tumor markers										
ER+/PR+/Her2-	11 (30.5%)	8 (17%)	8 (29.6%)	2 (18.1%)	0.07	4 (17.3%)	9 (15.7%)	9 (19.5%)	3 (20%)	0.34
ER+/PR+/Her2+	14 (38.8%)	23 (48.9%)	7 (25.9%)	2 18.1%)	0.01	4 (17.3%)	14 (24.5%)	14 (30.4%)	5 (33.3%)	0.08
ER-/PR-/Her2+	3 (8.33%)	5 (10.6%)	5 (18.5%)	5 (45.4%)	0.03	6 (26%)	8 (14%)	12 (16%)	4 (26.6%)	0.24
ER-PR-Her2-	2 (5.55%)	5 (10.6%)	1 (3.7%)	3 (27.2%)	0.68	2 (8.6%)	14 (24.5%)	7 (15.2%)	2 (13.3%)	0.76

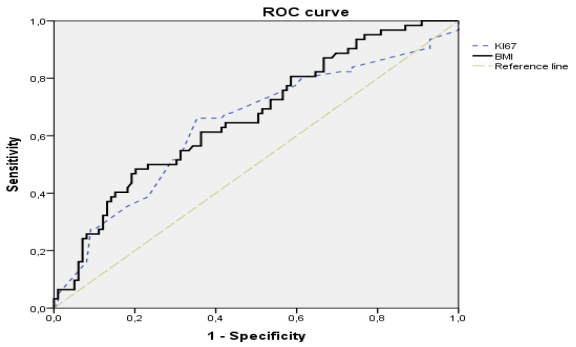

Figure 1. Receiver Operating Characteristic Curves using BMI and Ki-67 to Predict Grade III BC

Table 3. The Predicting Ability of BMI among BC Subtypes and according to Menopausal Status

	AUC (95% CI)		
	Total	Premenopausal	Postmenopausal
ER+	0.59 (0.49-0.69)	0.56 (0.43-0.70)	0.63 (0.49-0.76)
ER-	0.62 (0.49-0.74)	0.66 (0.43-0.89)	0.60 (0.45-0.74)
PR+	0.56 (0.46-0.66)	0.53 (0.40-0.67)	0.59 (0.44-0.74)
PR-	0.64 (0.53-0.75)	0.68 (0.46-0.9)	0.62 (0.49-0.76)
Her2+	0.59 (0.49-0.68)	0.53 (0.38-0.68)	0.64 (0.51-0.77)
Her2-	0.64 (0.53-0.76)	0.73 (0.57-0.89)	0.57 (0.41-0.73)
ER+PR+Her2-	0.58 (0.41-0.75)	0.70 (0.50-0.90)	0.46 (0.19-0.74)
ER+PR+Her2+	0.57 (0.44-0.70)	0.48 (0.31-0.66)	0.66 (0.48-0.84)
ER-PR-Her2+	0.60 (0.44-0.77)	0.67 (0.39-0.95)	0.56 (0.35-0.78)
ER-PR-Her2-	0.64 (0.44-0.84)	0.58 (0-1)	0.63 (0.41-0.86)

specific marker to predict grade III BC.

Discussion

BC is one of the most prevalent malignancies in women around the world (Jemal et al., 2011). The average age of occurrence of the BC in Tunisia reveals that the disease occurs a decade earlier, as compared with the Western countries (Chouchane et al., 2013). In the present study, mean age of cases was 50.9±11.9. By contrast, the average age of occurrence of BC among US white womens has been reported to be 61.0 years (Chouchane et al., 2013). The continuing rise of BC incidence has created an urgent need to develop strategies for its prevention. One of the few modifiable risk factors that may affect BC development is obesity (Amadou et al., 2013; Yaw et al., 2014). The prevalence of obesity has augmented in parallel to cancer, reaching epidemic proportions in many countries. In Tunisia, obesity is frequent among older women; its incidence is about 33.5% among all women and about 52.1% of women over 45 years (Belfki et al., 2013; Maatoug et al., 2013). Several studies have investigated the relationship between BC and obesity, yet the results have been mixed among ethnic groups (Amadou et al., 2013).

In this study, we investigated 262 Tunisian patients to evaluate the effect of BMI on pathological features of BC. Our results revealed that obesity is associated with larger tumor size and higher tumor grade in both premenopausal and postmenopausal women. These findings are consistent with studies conducted on African American (Zhu et al., 2005), Danish (Ewertz et al., 2011), Iranian (Kaviani et al., 2013) and Asian women (Amadou et al., 2013). However, an inverse association between BMI and BC risk, with a 7% reduction in risk per 5 kg m^{-2} increase in BMI was documented in premenopausal Caucasians womens (Renehan et al., 2008; Amadou et al., 2013). The variation observed between the ethnic groups may be explained by differences in body size and fat composition in different populations. Indeed, a study on the relationship between BMI and body fat in different population, revealed that Asian are different from Caucasians populations, this can be partly explained by differences in body build, i.e. differences in trunk-to-leg-length ratio or differences in slenderness (Deurenberg et al., 2002).

Additionally, our results revealed that lymph node metastasis are not more common in obese women compared to normal weight women. This observation was in accordance with the study conducted by Keskin and al (Keskin et al., 2013). Nevertheless, the association between obesity and higher risk of lymph node metastasis was reported by other groups (Porter et al., 2006; Singh et al., 2011; Kaviani et al., 2013).

The status of ER and PR in obese women was also a matter of controversy. Several studies conducted to evaluate the effect of BMI at time of diagnostic on histopathological features concluded that obese post-menopausal women develop more frequently ER/PR positive tumors (Biglia et al., 2013). However, others studies showed that obesity and overweight increases the risk of developing triple negative BC subtype, particularly for premenopausal women (Turkoz et al., 2013). Our results revealed that there is an association between BMI and ER-PR-Her2+ tumor subtype. Interestingly, when the data are stratified according to the menopausal status, a significant association of BMI with combined ER+PR+Her2+, ER-PR-Her2+ and ER+ BC tumors was observed for premenopausal women, whereas only ER+PR+Her2+ subtype is associated with BMI among postmenopausal patients. As the association between BMI and expression of ER and PR is a matter of controversy in literature, further studies must be conducted using large BC registry database to determine the impact of obesity on these important prognosis factors.

ROC curve analysis was used to determine the discriminative power of BMI, in comparison to Ki-67 proliferation index, to predict aggressive tumors at time of diagnostic (Kilickap et al., 2014). Our results demonstrate that BMI is as pertinent as Ki-67 in predicting high tumor grade. Hence, obesity could be considered as a reliable marker for agressive BC. The same observation was reported by other groups (Hajian-Tilaki et al., 2011). Recently, Santillan-Benitez et al have demonstrate that BMI, leptin, leptin/adiponectin ratio and CA 15-3 together are reliable biomarkers of BC (Santillan-Benitez et al., 2013). These findings imply to perform BC screening program in women with a higher BMI.

The mechanism by which obesity influences BC remains poorly understood. Several possible mechanisms have been suggested: *i*) Obese people often have increased levels of insulin and insulin-like growth factor-1 in their blood, which may promote the development of tumors (Belardi et al., 2013), *ii*) Adipose tissue produces hormones, called adipokines such as leptine and adiponectine, that

may stimulate angiogenesis, growth of malignant cells (Grossmann et al., 2010; Khan et al., 2013) and that may modulate anti-tumor immune response (Catalan et al., 2013) *iii*) Finally, obesity is associated with elevated levels of pro-inflammatory cytokines (Harvey et al., 2011) which generate a low grade chronic inflammatory state that may be involved on cancer development (Hanahan and Weinberg, 2011; Ferguson et al., 2013).

In conclusion, our results revealed that obesity is associated with larger tumor size and higher tumor grade and that BMI can be useful for predicting high grade tumors. As the prevalence of obesity in the world continues to raise, improvement in detection strategies, specific treatments and diet interventions are needed.

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