

1
2 **HEALTH RELATED QUALITY OF LIFE OF WOMEN WITH**
3 **GYNECOLOGICAL CANCER RECEIVING CHEMOTHERAPY**
4 **IN THE UNIVERSITY COLLEGE HOSPITAL, IBADAN.**

5
6 **ABSTRACT**
7

Aims: This study aim at assessing the health related quality of life of women with gynecological cancer on chemotherapy, to identify their major concern and to assess the relationship between health related quality of life with side effect of chemotherapy.

Study design: Cross sectional descriptive study on women with gynecological cancer on chemotherapy.

Place and Duration of Study: Radiation Oncology Department, University College Hospital Ibadan, between June 2018 and July 2018.

Methodology: Purposive sampling technique was used to select 117 women with gynecological cancer undergoing chemotherapy treatment at the University College Hospital, Ibadan. The instrument used was European Organization for Research and Treatment of Cancer core questionnaire (EORTC QLQ-C30).

Results: The mean age of participants is 48.8 years. Cervical cancer (69.2%) is the most prevalent gynecological cancer as revealed in this study. In sub-dimensions of the functional status scale the scores of cognitive and physical status was found higher while emotional and social status score were found lowest. Global health, majority of the respondents rated it good (82.1%). On the symptom scale, financial difficulty ranked the highest concern (88%). The most prevalent side effects of chemotherapy as experienced by the respondents in this study was nausea (69.2%), and vomiting (47.6%). There was a statistically significant association between health related quality of life and the prevalent side effect with ($p=0.015$). **Conclusion:** This study revealed that larger number of the respondents had good health related quality of life but majority experiences severe side effects. Nurses play a key role in the identification and treatment of the side effects of chemotherapy therefore

minimizing the side effect of chemotherapy may positively impact on patient's health related quality of life.

8

9 *Keywords:* Health related quality of life, Gynecological cancer, Chemotherapy, Side effect.

10

11 **INTRODUCTION**

12 Cancer is a major public health problem. It caused over 8 million deaths worldwide in 2013 and has
13 moved from the third leading cause of death in 1990 to the second leading cause behind
14 cardiovascular disease in 2013 (GBD Mortality and Causes of Death Collaborators, 2013). Three
15 decades ago cancer was more prevalent in the developed world but the burden is shifting significantly
16 to the developing countries (Sanni, Ocheke & Oyebode, 2013). Gynecological cancers are a frequent
17 group of malignancies in women, accounting for approximately 18% of all female cancers worldwide
18 (Goker, Guvenal, Yanikkerem, Turhan & Koyuncu, 2011). Gynecologic cancers are cancers that begin
19 in the reproductive organs, including the cervix, uterus, ovaries, vagina and vulva.

20 Approximately 84,000 new cases are diagnosed and about 28,000 deaths occur each year from
21 gynecologic cancer among women in the United States (United States cancer statistics, 2013). The
22 gynaecologic cancer burden in developing countries like Nigeria is huge primarily due to the high
23 incidence and mortality of cervical cancer (Agboeze, Ezenonu, Onoh, Nwali, Agwu & Rose, et al.,
24 2015).

25 After the diagnosis of gynecologic cancer, women are faced with the diagnosis itself, personal
26 interpretation of cancer, physical effects of the disease, long and short term side effects of the
27 treatment regimes and the reaction of family and friends (Pınar, Algier, Çolak & Ayhan, 2008; Özaras
28 and Özyurda, 2010). The management of patient with gynecological cancer mainly aims at prolonging
29 survival but modern therapy focuses on good survival combined with a good quality of life (QoL).
30 (Goker, et al., 2011). The mode of treatment of cancer which involves chemotherapy, radiotherapy
31 and Surgery influence the QoL of women extensively. Chemotherapy is a concentrated and repeated
32 treatment drug regimen, unlike surgery it has many adverse reactions including hair loss, nausea,
33 vomiting, fatigue and diarrhea; besides it requires extended periods of treatment and repeated
34 admissions to the hospital, which can eventually affect the QoL of patients with cancer. In oncology
35 chemotherapy is used as a front-line therapy, as an adjuvant to surgery or radiotherapy and even in
36 palliative care. However in a large majority of cases, despite initial reduction in tumor size, the vast

37 majority of cancers become unresponsive to chemotherapy (Skeel and Khleif, 2011) When
38 treatment can not result in cure, it should lead to an improvement of well-being and quality of life
39 (Weaver, Forsythe, Reeve BB, Alfano CM, Rodriguez JL, Sabatino SA, et al., 2012).

40 Quality of Life for patients is defined as “extent to which one’s usual or expected physical, emotional
41 and social well-being is affected by a medical condition or its treatment”. While Health-related quality
42 of life (HRQOL) is a subjective health status that focuses more on the impact of a perceived health
43 state on the ability to live a fulfilling life. For patients living with cancer, all aspects of life are
44 influenced negatively (Ferrell, Brearley, Pilling, and Molassiotis, 2013). Patients with cancer receiving
45 chemotherapy face some psychological problems- stress, anxiety, depression; some physiological
46 side-effects — hair loss, pain, tiredness, nausea, vomiting; some social side effects — social isolation,
47 role and function loss; and, eventually, a worsened quality of life. (Ferlay, Steliarova-Foucher, Lortet-
48 Tieulent, Rosso, Coebergh and Comber, 2012). Nowadays, the goal of cancer therapy is not only to
49 cure the cancer and increase the survival but also to minimize the symptoms relieve suffering, restore
50 functioning, or enhance the quality of life (Muliira, Salas and O'Brien, 2017). Higher quality of life
51 leads patients to complete therapy with the lowest harm, control experienced symptoms and
52 overcome these symptoms.

53 In a study by Goker, Guvenal, Yanikkerem, Turhan & Koyuncu (2011), on Health related Quality of
54 Life in women with Gynecological Cancer in Turkey it was revealed that Gynecological cancer and
55 treatment processes cause significant problems that have negative effects on physical, emotional,
56 social and role function aspects of QoL. Lívia and Sueli, in a similar study also shows that physical
57 domain was the most compromised, due to the toxicity of chemotherapy drugs administered, in
58 relation to cellular non-specificity, which can generate effects such as pain, fatigue, nausea and
59 vomiting, and additionally anorexia, hampering clients in their daily activities and thus reducing their
60 quality of life (Lívia and Sueli, 2010). Pain and fatigue were the most troublesome symptoms reported
61 in a study carried out by Jayesimi, Sofela and Rufai, (2007) on health related quality of life in women
62 with breast cancer, at the university college hospital Ibadan. While the highest functional score was
63 recorded on physical functioning scale and the lowest was on social functioning scale (Jayesimi et
64 al., 2007). Also, in a study on Quality of life among Zambian cervical cancer women post
65 chemo-radiotherapy it was revealed that Patients with advanced cervical cancer treated with

66 chemoradiotherapy experienced a favorable quality of life and treatment were considered worthwhile
67 by the majority, they also described problems with sexuality and marital relationships. Low education
68 and living without a partner were predictors of low quality of life (Chitashi, 2012).

69 Most of the gynecologic cancer patients presented with advanced cancer and generalized metastases
70 to various organ systems; as a result, most women had several symptoms and had been sick for
71 about 2 years before diagnosis, due to poor access to specialized health care, thus affecting their
72 quality of life (Khalil, Bellefqih, Sahli, Afif, Elkacemi & Elmajjaoui, 2015). Also, the problem of finances
73 as the cost of chemotherapy is usually unaffordable, and this is a major obstacle for many patients to
74 continue with the treatment (Akinyemiju, 2012). Financial difficulties ranked highest in a study carried
75 out at the university college hospital on health related quality of life in women with breast cancer
76 (Jayeisimi et al., 2007).

77 Over the years, studies have been done to assess quality of life (QoL) of patients living with cancers
78 on chemotherapy in different countries. Currently, there is paucity of such studies assessing HRQoL
79 of women with gynecological cancer on chemotherapy in south west and Nigeria at large. This has
80 prompted this study, which assessed the Health Related Quality of life in women with gynecologic
81 cancers on chemotherapy in University College Hospital Ibadan, Oyo State Nigeria.

82 **MATERIAL AND METHODS / METHODOLOGY**

83

84 The study used cross sectional descriptive design to elicit information from women with gynecological
85 cancers on chemotherapy at the University College Hospital, Ibadan. 117 women with gynecological
86 cancer on chemotherapy participated in the study. The data were collected between June and July
87 2018 from those who agreed to participate in the study. Eligibility criteria included] women diagnosed
88 with gynecological cancer on chemotherapy, aged 18 and above and willing to participate. After been
89 recruited, the women were given consent form explaining objectives, benefits and confidentiality of
90 the study and the women gave their consents. The instrument for the study was a self-structured
91 questionnaire and validated questionnaires. Section A assessed information on socio demographic
92 characteristics of the participants e.g age, sex, type of cancer, educational level etc this constitutes
93 questions 1 - 10. Section B assessed the health related quality of life in women with gynecological
94 cancer on chemotherapy, this section consist of questions 1-30 adapting the (EORTC) core
95 questionnaire version 3. (Aaronson et.al., 1993) It consist of three domain; domain A consist of 15
96 questions aimed at assessing the functioning, domain B aimed at assessing symptoms scale and

97 domain C aimed at assessing patient's perception on her global health status. The questionnaire was
 98 administered by the researcher and research assistants. Two Research assistants was trained on the
 99 data collection instrument and clarifications were provided by the researcher. Eligible persons at the
 100 radiation oncology ward and clinic were approached by the researcher and research assistance
 101 regarding their interest in participating. The questionnaire was administered by the researcher and
 102 research assistants. The data collected was analysed with statistical package for social sciences
 103 (SPSS, version 22).

104 **Result**

105
 106 The mean age was 48.8 years (± 10 years) with 28 and 68years being the minimum and maximum
 107 ages respectively. 74.4% were Christians while 25.6% of the respondents were Muslims. 65.8%
 108 were of Yoruba tribe, 27.4% of Igbo tribe while 6.8% were of Hausa tribe. 53% of the respondents
 109 were married, 22.2% were divorced and 6.8% were single. Cervical cancer was the most prevalent
 110 (81(69.2%) respondents) followed by ovarian cancer in 20(17.1%) respondents, endometrial cancer in
 111 8(6.8%) respondents while vaginal and vulva cancers occurred equally among 8(6.8%) respondents.
 112 Respondents had from 1 to 6 courses of chemotherapy with the mean course of chemotherapy being
 113 3times (± 1.5 times). Respondents' number of children was from 0 to 9 with the mean number of
 114 children being 4 children (± 2 children). 62.4% were traders, 20.5% were housewives, 13.7% were civil
 115 servants while 3.4% were students. 41.0% had a tertiary education, 39.3% had only secondary school
 116 education, 16.2% had only primary school education while only 3.4% of respondents had no formal
 117 education.

118 **Table 1: Respondent's demographic characteristics**

Variable	Frequency	Percentage (%)	Mean	Standard deviation	Minimum	Maximum
Age			48.79	10.04	28	68
28-34	16	13.7				
35-41	5	4.3				
42-48	39	33.3				
48.8-54	20	17.1				
55-61	20	17.1				
62-68	17	14.5				
Religion						
Islam	30	25.6				
Christianity	87	74.4				
Others	0	0.0				
Tribe						
Hausa	8	6.8				
Igbo	32	27.4				
Yoruba	77	65.8				

Others						
Marital status						
Single	8	6.8				
Married	62	53.0				
Divorced	26	22.2				
Widow	21	17.9				
Cancer type						
Ovarian	20	17.1				
Cervical	81	69.2				
Vaginal	4	3.4				
Vulva	4	3.4				
Endometrial	8	6.8				
Course of chemotherapy			3.03	1.50	1	6
1	14	12.0				
2	37	31.6				
3	33	28.2				
4	9	7.7				
5	12	10.3				
6	12	10.3				

119

120 Table 2 shows the mean, standard deviation, minimum and maximum values for each item under the
 121 component scales as well as that of the single items.

122 **Table 2: Health related quality of life of respondents**

Variable	Mean	Standard deviation	Minimum	Maximum
Functional scale				
Physical functioning	60.40	36.79	0.00	100.00
Role functioning	53.70	34.82	0.00	100.00
Emotional functioning	49.43	32.29	0.00	100.00
Cognitive functioning	61.60	33.56	0.00	100.00
Social functioning	36.75	33.59	0.00	100.00
Symptom scale				
Fatigue	56.41	28.01	16.67	100.00
Nausea and vomiting	51.19	31.90	0.00	100.00
Pain	50.85	29.18	16.67	100.00
Quality of life scale /global health status	63.03	18.09	33.33	83.33
Single items				
Dyspnea	25.64	34.57	0.00	100.00
Insomnia	50.14	33.80	0.00	100.00

Appetite loss	54.13	32.37	0.00	100.00
Constipation	41.60	31.84	0.00	100.00
Diarrhea	15.95	27.54	0.00	100.00
Financial difficulties	88.31	25.26	0.00	100.00

123

124 Table 3 shows that 82.1% of the respondents have a better health related quality of life while
125 17.9% has a worse health related quality of life.

126

127 **Table 3: Categories of respondents' health related quality of life**

Variable	Frequency	Percentage (%)
Health related quality of life		
Better	96	82.1
Worse	21	17.9

128

129 **Association between the side effects of chemotherapy and health related quality of**
130 **life of women with gynecological cancers on chemotherapy.**
131

132 Table 4, the p-value 0.015 is less than 0.05 and it can therefore be concluded that
133 there is significant association between health related quality of life and prevalent
134 side effects experienced by women on chemotherapy. Therefore, the null hypothesis
135 is rejected.

136 **Association between the side effects of chemotherapy and health related quality of**
137 **life of women with gynecological cancers on chemotherapy.**

138 Table 4

Variable	Prevalent side effects		X ²	P-value
	Mild	Severe		
Quality of life			8.434	0.015
Better	29(24.8%)	67(57.3%)		
Worse	0(0.0%)	21(17.9%)		

139

140 **DISCUSSION**

141 The ages of respondents ranges between 28 and 68years being the minimum and maximum ages
142 respectively, with mean age of 48.8 years (± 10 years) this is in agreement with findings from a similar
143 study by Livia and Sueli, (2007) with a mean age of 48.4 (± 12.0) years. Age has been reported to be
144 a single predictor of cancer development. Risk for the development of cancer begins to increase at 40
145 years of age and then increase rapidly at age 50years (American cancer and Society, 2004).

146 In this study, gynaecologic cancer includes cervical cancer, ovarian cancer, Endometrial cancer, vulva
147 and vagina cancer. Cervical cancer was the most prevalent (69.2%) respondents followed by ovarian
148 cancer in (17.1%) respondents, endometrial cancer in (6.8%) respondents while vaginal and vulva
149 cancers occurred equally among (3.4%) respondents, this report is in agreement with a large review
150 carried out in Lagos and Ibadan (South West Nigeria) in 2011 showed that cervical cancer was
151 second only to breast cancer as the commonest cancer in the region (Durowade, et al., 2012). The
152 pattern from Aminu Kano Teaching hospital in the largest metropolis in the north west of the country
153 equally shows that cervical cancer is the commonest Gynaecologic malignancy in women. According
154 to GLOBOCAN 2012, cervical cancer is the 4th commonest cancer in women and the 7th overall
155 worldwide. Its highest incidence occurs in less developed areas of the world where 85% of the cases
156 now occur (Cancer Institute, 2013).

157 In this study, the subdimensions of the functional status scale were evaluated, the mean of cognitive
158 and physical score was found higher while emotional and social functional subdimensions score were
159 found lowest in women with gynecological cancer on chemotherapy. Similarly, a study in Turkey,
160 which evaluated QoL of women using EORTC QLQ-C30 scale, stated that emotional (49.55±32.42)
161 aspects of QoL were mostly affected among the functional parameters and cognitive function
162 (66.33±27.45) was found higher (Pinar et al., 2008). The report is also in line with a result from a
163 similar study by Goker (2011) the mean of cognitive score was found higher than other dimensions
164 and emotional score was the lowest score in women with gynecologic cancer. It was stated in their
165 study that the low social functioning score, and especially emotional functions have been observed to
166 decrease significantly in the women with gynecological cancer and the findings indicates the impaired
167 QoL in cancer patients (Goker, 2011). In Nigeria, families, parental, and friends support is at quite a
168 low level, some see cancerous disease as a hopeless case thereby abandoning their relations with
169 such disease at such a critical state thus making an immense contribution to the impaired social and
170 emotional well-being. It was also stated in Goker et al., study that Cancer diagnosis, a long treatment
171 process and obscurity keep the patients away from social life and lead to disturbances in
172 interpersonal relationships resulting into low social functioning.

173 Regarding self-rated health, most of the respondents (63.03 ±18.09) rated it as very good or good and
174 considered that they are satisfied with it. Similarly Sueli and livia 2001, reported high score for global

175 health of respondents in their study on Quality of Life in Women with Gynecologic Cancer in Turkey. It
176 was stated in their study that high score of global health result indicates that, in view of the prospect
177 of progress of a chronic disease, they are satisfied with the moment they are experiencing. The QoL
178 as seen in this study is higher than that reported by Sueli and Livia this may be as a result of racial
179 difference. The result is contrary to what was obtained in a study on the Quality of Life in Cancer
180 Patients undergoing Chemotherapy by Dehkordi et al., (2009) their findings show that the Quality of
181 life (QoL) was fairly favorable in majority (66%) of the patients.

182 In relation to the symptom scale out of the 96 respondents with a better quality of life, 33 has mild
183 symptom with good functioning while 63 has severe symptoms with poor functioning. All the 21
184 respondents with worse quality of life have severe symptom and poor functioning. Despite the severe
185 symptoms experienced with poor functioning by majority, they still claimed to have good quality of life
186 this could be related to the fact that Nigerians are very strong and still claim to be fine in the face of
187 hardship.

188 On the symptom scale, financial difficulty ranked the highest followed by fatigue, pains, loss of
189 appetite, nausea and vomiting (88%,56%,54%,51% and 50%) respectively. It was also observed that
190 financial difficulties ranked highest in a study carried out at the university college hospital on health
191 related quality of life in women with breast cancer (Jayeisimi et al., 2007). The problem of finances is
192 a major cause of health deterioration as the cost of chemotherapy is usually unaffordable, and this is
193 a major obstacle for many patients to continue with the treatment (Akinyemiju, 2012). The most
194 experienced symptoms as its been reported in the literature for cancer patients, fatigue is the most
195 significant problem affecting the daily activities and life (Hoskins et al., 1997). In this present study,
196 fatigue score was found second highest for women with gyneacological cancer on chemotherapy.
197 Pain and fatigue were the most troublesome symptoms reported in a similar study carried out by
198 (Jaiyesimi et al., 2007). There was a statistically significant association between the prevalent side
199 effects and health related quality of life of women with gyneacological cancer on chemotherapy
200 ($p=0.015$). This study revealed that larger number of the respondents had good health related quality
201 of life but majority experiences severe side effects of chemotherapy.

202 **CONSENT**

203 Informed consent form was obtained from all respondents before administering the questionnaires.

204 ETHICAL APPROVAL

205 Ethical approval sought and obtained from the joint University of Ibadan/University College Hospital
206 (UI/UCH) ethical review board.

207 CONCLUSION

208 This study revealed that larger number of the respondents had good health related quality of life but
209 majority experiences severe side effects. Nurses play a key role in the identification and treatment of
210 the side effects of chemotherapy therefore minimizing the side effect of chemotherapy may positively
211 impact on patient's health related quality of life, and there is need for regular assessment of health
212 related quality of life of women with gynecological cancer because measuring the impact of cancer
213 and its treatment on patients' quality of life is being recognised as an important outcome measure.

214

215 REFERENCES

- 216 Aaronson N.K, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez N.J, Filiberti et al. The European
217 Organisation for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in
218 international clinical trials in oncology. *Journal of the National Cancer Institute*. 1993; 85: 365-376.
219 American Cancer Society Cancer Facts and Figures. Atlanta: US Department of Health and Human
220 Services, Centers for Disease Control and Prevention and National Cancer Institute. 2013.
- 221 Agboeze J, Ezenonu P.O, Onoh R.C, Nwali M.I, Agwu M.R, Egbuji C.C. Frequency and Pattern of
222 Gynecological Cancers in Federal Teaching Hospital, Abakaliki, Nigeria. *Journal of basic & Clinical
223 reproductive Sciences*. 2015; 4(2).
- 224 Goker T, Guvenal E, Yanikkerem A, Turhan F.M, Koyuncu. Quality of Life in Women with Gynecologic
225 Cancer in Turkey. *Asian Pacific J. Cancer Prev*. 2011; 12, 3121-3128.
- 226 Akinyemiju TF. Socio-economic and health access determinants of breast and cervical cancer
227 screening in low-income countries: Analysis of the World Health Survey. 2012
- 228 Chitashi N.S. Quality of life in Zambian cervical cancer women post chemo-radiotherapy (Unpublished
229 masters' dissertation). South Africa: University of Johannesburg; 2012.
- 230 Dehkordi A, Heydarnejad M.S, Fatehi D. Quality of life in cancer patients undergoing chemotherapy.
231 *Oman Medical Journal*. 2009; 24: 204-207.

- 232 Durowade K.A, Osagbemi G.K, Salaudeen A.G, Musa O.I, Akande T.M, Babatunde O.A. et al.
233 Prevalence and risk factors of cervical cancer among women in an urban community of Kwara State,
234 north central Nigeria. *J. Prev. Med. Hyg.* 2012; 53(4): 213-9.
- 235 Farrell C, Brearley S.G, Pilling M, Molassiotis A. The impact of chemotherapy related nausea on
236 patients' nutritional status, psychological distress and quality of life. *Support Care Cancer.* 2013; 21: 59-
237 66.
- 238 Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh J.W, Comber H. *et al.* Cancer
239 incidence and mortality patterns in Europe: Estimates for 40 countries in Europe. *Int. J. Cancer.* 2013;
240 49: 1374-403.
- 241 Ferlay J, Shin H.R, Bray F, Forman D, Mathers C, Parkin D.M. Estimates of worldwide burden of cancer
242 in 2008: GLOBOCAN 2008. *Int. J. Cancer.* 2010; 127: 2893-917.
- 243 GBD. Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-
244 cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the
245 Global Burden of Disease Study. *Lancet.* 2015; 385 (9963): 117–171.
- 246 Khalil J, Bellefqih S, Sahli N, Afif M, Elkacemi H, Elmajjaoui S, *et al.* Impact of cervical cancer on quality
247 of life: Beyond the short term (results from a single institution): Quality of life in long-term cervical
248 cancer survivors: Results from a single institution. *Gynecol. Oncol. Res. Pract.* 2015.
- 249 Jaiyesimi A.O, Sofela E.A, Rufai A.A. Health related quality of life and its determinants in Nigerian
250 breast cancer patients. *Afr. J. Med. Sci.* 2007; 36: 259-65.
- 251 Lívia L. R. J, Sueli R. Evaluation of the Quality of Life of Gynecological Cancer Patients. Submitted to
252 *Antineoplastic Chemotherapy.* 2010; 18 (5): 849-55.
- 253 Muliira R.S, Salas A.S, O'Brien B. Quality of life among female cancer survivors in Africa: An integrative
254 literature review. *Asia Pac Journal Oncol. Nurs.* 2017; 4: 6-17.
- 255 Özaras G, Özyurda F. Quality of life and influencing factors in patients with gynecologic cancer
256 diagnosis at Gazi University, Turkey. *Asian Pac J. Cancer Prev.* 2010; 11: 1403-8.

- 257 Pınar G, Algier L, Çolak M, Ayhan, A. Quality of life in patients with gynecologic cancer. *Int. J. Hematol*
258 *Oncol.* 2008; 3: 141-9.
- 259 Sanni O, Ocheke A, Oyebode T, Jonah M, Nyango D, Silas O, Sagay S. of gynecological malignancies
260 in Jos. *Tropic j. Obstetgynecol.* 2013; 30 (1).
- 261 Skeel R.T, Khleif S.N. *Handbook of cancer chemotherapy: Lippincott Williams & Wilkins.* 2011.
- 262 US Cancer Statistics Working Group, United States cancer statistics: Incidence and mortality web-
263 based report. 2013.
- 264 Weaver K.E, Forsythe L.P, Reeve B.B, Alfano C.M, Rodriguez J.L, Sabatino S.A, et al. Mental and
265 physical health-related quality of life among US cancer survivors: population estimates from the 2010
266 National Health Interview Survey. *Cancer Epidemiology Biomarkers & Prevention.* 2012; 21(11): 2108-
267 17.