ORIGINAL RESEARCH ARTICLE
pISSN09763325 | eISSN22296816
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www.njcmindia.com
DOI: 10.55489/njcm.130920222120

Breast Cancer Is Significantly Associated with Cancers in The First- and Second-Degree Relatives in Ethnic Mizo-Mongoloid Population, Northeast India

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ABSTRACT

Background: High incidence of breast cancer among the endogamous Mizo-Mongoloid tribe stresses the need to explore the disease pertaining to the family history as well as other risk factors. This study investigates the association of risk factors and inherited diseases with breast cancer.

Methodology: The study includes 426 unrelated breast cancer cases and 810 healthy controls of female Mizo ethnicity. Association between reproductive history, lifestyle/ dietary habits, tobacco and alcohol exposures, family history in relation to cancer and inheritable diseases was assessed by univariate logistic regression using Chi-square tests and multivariate analyses using Cox regression.

Results: Age at diagnosis was highest between 41 to 50 years. Consumption of fermented pork fat, smoked food and Smoke-less tobacco, lower intake of vegetables/ water, having a first/ or second degree relative with cancers and inheritable diseases were found to be the major risk factors. Certain known factors were also acting as confounding factors.

Conclusions: The present study reveals that Mizo women with first- and second-degree relatives of breast cancer, various other cancers and inheritable diseases have increased risk of breast cancer. This study also highlights the importance of analysing genetic factors which can aid in early detection of inherited risk factors.

Key-words: Dietary habits, Family history, Inheritable disease, Lifestyle habits, Smoked and fermented food

INTRODUCTION

Breast cancer is a multifactorial disease attributed by genetics and epigenetic factors[1]. Cancer related gene modifications varies based on the ancestry, ethnicity and evolutionary pressures. The relationship between ethnic disparity and single nucleotide polymorphisms linked to cancers and several other diseases have been studied[2]. Of all the new cases, breast cancer is the highest and is the leading cause of mortality among females (Globocan, IARC 2020).

The Mizo-Mongoloid tribal population, in the southernmost part of north-eastern India, with unique lifestyle factors have shown increasing trend of breast cancer incidence. Mizoram state has high incidence of different types of cancers (gastric, oral, lung, breast) even though it has a small area with a population of

How to cite this article: Zodinpuii D, Pautu JL, Zothankima B, Khenglawt L, Lallawmzuali D, Lalmuanpuii R, zuali L, Ralte L, Muthukumaran RB, Varma AK, Zothanzama J, Kumar NS. Breast Cancer Is Significantly Associated with Cancers in The First- and Second-Degree Relatives in Ethnic Mizo-Mongoloid Population, Northeast India. Natl J Community Med 2022;13(9):606-611.
DOI: 10.55489/njcm.130920222120

Financial Support: Dept of Biotechnology, GOI, New Delhi under Advanced Level State Biotech Hub at Mizoram University
Conflict of Interest: None declared
Date of Submission: 29-05-2022
Date of Acceptance: 27-07-2022
Date of Publication: 30-09-2022
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about 1.332 million in 2021 (PBCR, 2021). The state has been ranked as the highest tobacco consuming state in India, which is one of the evidence for the higher incidence of cancer in Mizoram. Besides cigarette smoking, usage of smokeless tobaccos which are in the form of powder, either dry (sahdah) or moist (khaini) and in liquid form ('*Tuibur*') are very popular. Sahdah and khaini are placed inside the lower or upper lip or in between the cheek and gums, while tuibur is kept in the mouth and spitted out later. The unique dietary custom such as fermented pork fat called *sa-um* and smoked food constitutes the major part in Mizo traditional food and is another questionable factor for the unenviable incidence of cancer[3]. Existing literature on *sa-um* focuses on the microbiome, but since it is derived from the pork fat, its content is mostly high saturated fats or cholesterol representing adverse health effect[4]. It has also been a stringent tradition to practice marriages within the Mizo community only for many centuries and endogamy is practiced to date[5].

The social and the built neighbourhood and the toxicology of the environment that a person is brought up in plays a significant role in the risk of breast cancer[6]. We hypothesize that the family history of genetically linked diseases will play a major role apart from the epidemiological or environmental risk factors for breast cancer in this small high-risk endogamous population. The present study focuses on family history, demography, life style and food habits that could potentially identify the risk factors for development of breast cancer among the women of Mizo tribal population in Northeast India.

METHODOLOGY

The study was conducted in 2018 from 426 confirmed breast cancer patients recruited in Civil Hospital Aizawl, Mizoram and Mizoram State Cancer Institute, Mizoram from the year 2013 – 2017. Female healthy controls were age-matched with the patient group and belonged to the same ethnic group and the sample size was increased to 810 for more statistical power in the analysis of the risk factors.

The participants were explained about the aim of the study, and with their consent, personal interview was conducted on a questionnaire designed in bilingual structure (English and Mizo local language). Only local ethnic patient histologically confirmed breast cancer by an experienced pathologist of all ages from different hospitals of Mizoram, with and without family history of breast cancer were included in the study.

Self-declared healthy controls (at the time of sampling) without any breast cancer history were recruited for this study. Male breast cancer patients were excluded from the study. Individuals with any history of other cancers were excluded from the study for both cases and controls. Study inclusions for cases are: 1) breast cancer patient of all ages that are histologically confirmed (Fine- Needle aspiration cytology) by a pathologist. 2) Only local ethnic patients, with and without family history of breast cancer from different hospitals of Mizoram.

Inclusion criteria for control groups are: 1) Female healthy controls of age-matched with the patient group. 2) Belong to the same ethnic group. The exclusion criteria for both the cases and controls groups are: 1) Individuals with any history of other cancers. 2) Male breast cancer. 3) Individuals belonging to other ethnic groups. The participants were explained about the aim of the study, and with their consent, personal interview was conducted on a questionnaire designed in bilingual structure (English and Mizo local language). The clinical and pathological reports of the patients were obtained from their medical records.

Since the participants self-reported their reproductive history, tobacco and alcohol usage histories, our study might be subjected to recall bias. However, professionally trained medical laboratory technicians were employed to carry out interviews and the questionnaire used Likert scale and dichotomous style and was designed to reduce the chances of potential recall bias. Questionnaire comprises the demographic information, reproductive, environmental factors and family history in relation to cancers and other inheritable diseases. Reproductive history such as age at marriage, marital status, age at menarche, age at menopause, parity, age at first delivery, number of children, breast feeding, duration of lactation, use of oral contraceptive pills and abortion were taken into account. Environmental factors include lifestyle habits (exercise, sleeping hours and night duty), dietary habits (amount of intake of pork, fish, chicken, beef, fruits, vegetables, *sa-um*, smoked food, salt, water and oil), tobacco (sahdah, khaini, *tuibur* and cigarette) and alcohol intake. It is undeniably difficult for cases and control to estimate the exact amount of consumption and/or use of dietary habits for which the answers were categorized into a Likert scale, such as "Never", "Thrice a week", or "Everyday". As for tobacco and alcohol history, the questions were of dichotomous style of whether using or not. Formaldehyde used as a preservative for fish was estimated on fish samples obtained from four different sources such as Mizoram, Silchar, Burma and Andhra Pradesh[7].

The present work has been approved by the ethical committees of Civil Hospital, Aizawl (B.12018/1/13-CH(A)/IEC/33 dtd.15/10/2014) and Institutional Human Ethical Committee, Mizoram University.

Statistics:

Frequency distribution of the study samples (cases and controls) for age was calculated. Univariate logistic regression analyses in Chi-square test were used to assess the association between independent risk factors and breast cancer. Independent factors that are found significant in the univariate analysis

were included in the multivariate analysis among case-control subjects by using binary logistic regression[8]. Univariate and Multivariate logistic regression analyses was conducted using the IBM Statistical Package for Social Sciences (SPSS), software version 22.0 for Windows. The odds ratio and confidence interval were calculated using MedCalc Statistical Software version 20.113 (https://www.medcalc.org/calc/odds_ratio.php).

RESULTS

The study includes breast cancer cases age ranging from 20 - 91 years old women. Majority of breast cancer incidence was observed at age between 41-50 years and the mean age was 50 years (Supplementary Figure 1). In the univariate logistic regression for several factors under reproductive history, it is observed that marital status, late age at menopause, breast feeding, and shorter duration of lactation were found to increase breast cancer risk (Supplementary Table 1).

In the univariate analysis for life style habits, an association was observed between lack of physical exercise, shorter sleep duration (less than 6 hours) and night shift work with increased breast cancer risk (Supplementary Table 2). However, in the univariate analysis for different factors of dietary habits, regular or heavy intake of pork, fish, beef, smoked food, and lack of vegetables and water (less than 1 liter/ day) intake were found to increase the risk of breast cancer (Supplementary Table 3). The fish from Andhra Pradesh was observed to have the highest concentration (µg/g Tissue) of formaldehyde (3.17 ± 0.43), followed by Silchar (1.52 ± 0.60), Burma (0.28 ± 0.06) and Mizoram (0.17 ± 0.04).

Consumption of tobacco in smokeless form, 'Sahdah' and 'khaini' and in liquid form, *'tuibur'* were found to be significantly associated in the development of breast cancer (Supplementary Table 4). Having a 1st and/or 2nd degree relative with various types of cancer and having inheritable diseases such as diabetes and hypertension were observed to have an association with increased risk of developing breast cancer (Table 1).

Multivariate analysis was performed for the factors that showed an independent association with increased risk for breast cancer from the univariate analysis. High consumption of smoked food and 'khaini', lack of vegetables and water intake, having a 1st and 2nd degree relatives with breast cancer, 1st and 2nd degree relatives with other cancer, and also having inheritable diseases were observed to be the major risk factors for breast cancer incidence among Mizo women. Furthermore, late age at menopause, shorter duration of lactation, lack of physical exercise was observed to be the confounding factors for the development of breast cancer. (Table 2).

Table 1: Family History of diseases and their risk of breast cancer

Risk factors	Cases N (%)	Controls N (%)	OR (95% CI)	p-value
1st and 2nd degree relatives with Breast Cancer				
Yes	93 (21.8)	86 (10.6)	Ref	<0.0001
No	333 (78.2)	724 (89.4)	2.3511 (1.70 - 3.23)	
Total	426 (100)	810 (100)		
1st and 2nd degree relatives with Other Cancers				
Yes	290 (68.1)	488 (60.2)	Ref	0.0069
No	136 (31.9)	322 (39.7)	1.4070 (1.09 - 1.80)	
Total	426 (100)	810 (100)		
Inheritable Disease				
1- 4	150 (35.2)	165 (20.4)	Ref	<0.0001
No	276 (64.8)	645 (79.6)	2.1245 (1.63 – 2.76)	
Total	426 (100)	810 (100)		

Table 2: Multivariate logistic regression for breast cancer associated risk factors

Risk Factors	Odds Ratio (95% CI)	p value
Smoked Food (high)	1.72 (1.070- 2.779)	< 0.025
Khaini use	2.800 (1.726- 4.543)	< 0.0001
Vegetables (less)	1.98 (1.329- 2.977)	< 0.001
Water intake (less)	1.640 (1.178- 2.283)	< 0.003
1st and 2nd degree BC relative	2.458 (1.671- 3.618)	< 0.00001
Inheritable Diseases	2.693 (1.925- 3.769)	< 0.00001
Age at Menopause (older)	0.35 (0.260- 0.488)	< 0.00001
Lactation Duration (shorter)	0.54 (0.395- 0.756)	< 0.00001
Physical Exercise (low)	0.50 (0.345- 0.742)	< 0.00001

DISCUSSION

The study carried out in the Mizo tribal population revealed a unique dietary and life style habits across the case-control study. An interesting feature is that the sub-tribes have inter-marriages amongst themselves and the Mizo population follows endogamy. In this study, association between breast cancer risk with reproductive history, life style/ dietary habits, and family history in relation to cancers and other inheritable diseases were analyzed. The peak breast cancer incidence age in developed countries is above 50 years, whereas in our study the maximum number of cases diagnosed were between the age of 41-50 years. Breast cancer incidence in the studied population is observed from 20 years to 91 years (Mean = 50). The breast cancer incidence age pattern is found to have very much similarity observed in other Indian states and as well as other countries with breast cancer incidence age range from 18 to 70 years (mean= 49.3)[9].

Smoked food was found to be positively associated with increased risk of breast cancer. PAHs can be introduced into the body through the consumption of smoked/grilled/ roasted foods and accumulated in the mammary and fat tissues and PAHs covalently bind to DNA of epithelial cells forming PAH-DNA adducts[10]. The association between breast cancer risk and smoked or grilled food is limited. Studies on the population of Long Island, New York suggested an elevated 31% risk of all-cause mortality among breast cancer patients with high pre- and post- diagnosis intake of smoked food.[3] Several case- control studies have shown the association of dietary fats with breast cancer risk. Particularly, saturated fats may increase endogenous estrogen production which is the main factor for determining breast cancer risk[11]. Whereas, another study found no association between dietary fats and breast cancer risk[12]. Differences in these results observed may be attributed to low fat intake among different populations, measurement error and other confounding factors including individual's body fat content, antioxidants, fiber and high energy diet intake that might alter the exact association of different classes of fats and breast cancer[11].

Less vegetables and water intake were also found to be significantly associated with breast cancer in this study. A Cross-sectional study has reported higher chance of breast cancer development for women with minimal vegetable intake[13]. Dehydration leads to impairment of cellular function leading to the inability to remove harmful toxins that may result in cancer[14].

In our study, consumption of smokeless tobacco in moist form 'Khaini' and liquid form '*Tuibur*' were found to be positively associated with breast cancer risk. Different investigators have reported cancer incidence risk and use of smokeless tobacco[15,16]. An age-old tradition among the Mizo population is the practice of *Jhum* or shifting cultivation (slash and burn of forests) which necessitates the need to stay in the farm overnight. The practice of smoking among the family members started, in these agricultural lands, to ward off mosquitos and this made the individuals to indulge in smoking from a young age which continued generations after generations. A generation cohort study revealed the significant association of an increased breast cancer risk in women who had been smoking since adolescence or perimenarcheal ages, and this risk was increased with the presence of the breast cancer in the family[6].

In this study, about 45% of the first-degree relatives of breast cancer patients were diagnosed with various cancers such as gastric, lung, oesophagus, liver, uterus, breast, etc. and was observed that having a 1st and/ or 2nd degree relative with breast cancer and various other cancers to be potential risk factors for the development of breast cancer. Our observation is fully supported by earlier studies suggesting the relative risk of developing breast cancer for an individual with 1st degree relative with breast cancer[17]. Studies conducted in UK cohort observed an increase breast cancer risk with a greater family history score suggesting a 2.5-fold increased risk of breast cancer among women with two or more relatives diagnosed with breast cancer[18].

In this study, having an inheritable disease such as diabetes and hypertension were observed to increase the chances of developing breast cancer. Diabetes and hypertension were commonly found within the family of several breast cancer patients. Three large meta- analysis concluded that there is a 20% increased risk of breast cancer among diabetic women of Europe, America and Asia[19,20]. However, in contrast to our findings, a meta- analysis on Hispanic and African American women observed only little evidence of association between diabetes and increased breast cancer risk. The potential influence of diabetes on breast cancer risk may vary in different ethnic groups due to the nature of visceral fat and adipokines that have been earlier hypothesized to function as effect modifiers in obesity-related diseases[19].

Furthermore, a meta- analysis study for hypertension and breast cancer risk suggested a 15% increased risk of breast cancer for postmenopausal hypertensive Asian women. It is assumed that: 1) hypertension and breast cancer may share the pathophysiological pathway mediated by adipose tissues causing chronic inflammation which might further lead to an increased risk of both the diseases, 2) hypertension may block or alter apoptosis, thereby affecting cell turnover regulation and increase breast cancer risk[21].

As observed, the confounding risk factors are late age at menopause, shorter duration of lactation and lack of physical exercise among the Mizo women. Late age at menopause is found to be one of the major breast cancer risk factors, and this observation is well established for different populations. Elevated

and extended exposure of ovarian hormone may be the probable reason[22]. Breastfeeding is said to have a protective effect by decreasing the intensity and frequency of ovulation, which in turn maintains the low level of estrogen[23]. Literature review has concluded that there is a higher degree of protective effect against breast cancer for women with longer duration of lactation in different ethnic populations[24]. A two-fold increased risk of TNBC was observed for parous women who never breast-fed as compared to nulliparous women. However, women experienced no increased risk when breast feeding duration lasts for >24 months[25]. According to the World Cancer Research/ American Institute for Cancer Research in 2007, a probability of inverse association was observed between physical activity and postmenopausal breast cancer[26]. A number of studies had suggested the protective role of physical activity against breast cancer risk which can be attributed to changes in sex hormone levels, adiposity, immune function and insulin-related hormones[27].

Most of the fish consumed in Mizoram imported from Andhra Pradesh which has the highest concentration of formaldehyde (3.17 µg/g Tissue) as compared to fish from different sources available in the state. Consumption of fish showed independent association with the increased risk of breast cancer and is attributed to the consumption of fish with high concentrations of formaldehyde (HCHO). Formaldehyde has been grouped as a Group 1 carcinogenic to humans by International Agency for Research on Cancer (IARC 2004). It has been shown to be genotoxic as well as carcinogenic by forming DNA-protein cross-links[28]. According to the United States Environmental Protection Agency (EPA), formaldehyde below 0.2 µg/g body weight per day is non-toxic (Noordiana et al. 2011)[29].

The confounding risk factors for breast cancer were low intake of vegetables and water, late age at menopause, shorter duration of lactation and lack of physical exercise which may increase the chance of developing breast cancer. Our study shows protective effect by some of the risk factors which needs to be investigated further to rule out any potential sampling bias.

CONCLUSION

The present epidemiological study had revealed that ethnic dietary/ life style habits such as smoked food, and local smokeless tobacco ('Khaini' and '*Tuibur*') play an important role in breast cancer progression. Having life style diseases such as diabetes and hypertension, 1st and/ or 2nd degree relatives with breast cancer and various cancer types were found to contribute the risk of breast cancer among the Mizo tribal women of Mizoram, India. Routine genetic screening for early detection to those with the inheritable risk factors will also help women to avert the breast cancer risk. This study reveals the importance and the need to have genetic study of different racial/ethnic populations for the prevention and diagnosis of cancer, especially targeting minorities where disparities are known to be present.

ACKNOWLEDGEMENT

We thank all the Breast cancer patients and the healthy individuals who helped us take the first step in building the foundation for breast cancer research in Mizoram tribal Society. The authors thank the Department of Biotechnology (DBT), Govt. of India, New Delhi for the infrastructure and support for this study through Advanced Level State Biotech Hub (BT/NER/143/SP44475/2021) at Mizoram University.

REFERENCES

1. Sirisena ND, Adeyemo A, Kuruppu AI, et al. Genetic determinants of sporadic breast cancer in Sri Lankan women. *BMC Cancer.* 2018;18(1):180.
2. Özdemir BC, Dotto GP. Racial Differences in Cancer Susceptibility and Survival: More Than the Color of the Skin? *Trends Cancer*. 2017;3(3):181-197.
3. Parada H Jr, Steck SE, Bradshaw PT, et al. Grilled, Barbecued, and Smoked Meat Intake and Survival Following Breast Cancer. *J Natl Cancer Inst*. 2017;109(6):djw299.
4. De Mandal S, Singh SS, Muthukumaran RB, et al. Metagenomic analysis and the functional profiles of traditional fermented pork fat 'sa-um' of Northeast India. *AMB Express.* 2018;8(1):163.
5. Pachuau L, Zami Z, Nunga T, et al. First-degree family history of cancer can be a potential risk factor among head and neck cancer patients in an isolated Mizo tribal population, northeast India. *Clin Epidemiology Glob Health.* 2002;13:100954.
6. Jones ME, Schoemaker MJ, Wright LB, et al. Smoking and risk of breast cancer in the Generations Study cohort. *Breast Cancer Res*. 2017;19(1):118.
7. Jaman N, Hoque MS, Chakraborty S, et al. Determination of formaldehyde content by spectrophotometric method in some fresh water and marine. *Int J Fish Aquat*. 2015;2(6):94-98
8. Ghatak S, Yadav RP, Lalrohlui F, et al. Xenobiotic pathway gene polymorphisms associated with gastric Cancer in high risk Mizo-mongoloid population, Northeast India. *Helicobacter*. 2016;21:523–35.
9. Palachandra A, Ishawaraprasad GD, Sreelatha CY, Sumana M. Risk factors associated with carcinoma breast: a case control study. *Int Surg J*. 2017;4(9):3136-3140.
10. Gamboa-Loira B, López-Carrillo L, Mar-Sánchez Y, et al. Epidemiologic evidence of exposure to polycyclic aromatic hydrocarbons and breast cancer: A systematic review and meta-analysis. *Chemosphere*. 2022;290:133237.
11. Khodarahmi M, Azadbakht L. The association between different kinds of fat intake and breast cancer risk in women. *Int J Prev Med*. 2014;5(1):6-15.
12. Binukumar B, Mathew A. Dietary fat and risk of breast cancer. *World J Surg Oncol*. 2005;3:45.
13. Kooshki A, Moghaddam MY, Akbarzadeh R. Study of fruit and vegetable intake in breast cancer patients in the city of Sabzevar. *Electron Physician.* 2016;8(9):3011-3014.
14. Keren Y, Magnezi R, Carmon M, Amitai Y. Investigation of the Association between Drinking Water Habits and the Occurrence of Women Breast Cancer. I*nt J Environ Res Public Health.* 2020;17(20):7692.

15. Kendrick PJ, Reitsma MB, Abbasi-Kangevari M, et al. Spatial, temporal, and demographic patterns in prevalence of chewing tobacco use in 204 countries and territories, 1990–2019: a systematic analysis from the Global Burden of Disease Study 2019. *Lancet Public Health.* 2021;6:e482–99.

16. Gupta S, Gupta R, Sinha DN, Mehrotra R. Relationship between type of smokeless tobacco and risk of cancer: A systematic review. *Indian J Med Res.* 2018;148(1):56-76.

17. Mahdavi M, Nassiri M, Kooshyar MM, et al. Hereditary breast cancer; Genetic penetrance and current status with BRCA. *J Cell Physiol.* 2019;234(5):5741-5750

18. Brewer HR, Jones ME, Schoemaker MJ, et al. Family history and risk of breast cancer: an analysis accounting for family structure. *Breast Cancer Res Treat.* 2017;165(1):193-200.

19. Maskarinec G, Fontaine A, Torfadottir JE, et al. The Relation of Type 2 Diabetes and Breast Cancer Incidence in Asian, Hispanic and African American Populations-A Review. *Can J Diabetes*. 2018;42(1):100-105.

20. Hardefeldt PJ, Edirimanne S, Eslick GD. Diabetes increases the risk of breast cancer: a meta-analysis. *Endocr Relat Cancer.* 2012;19(6):793-803.

21. Han H, Guo W, Shi W, Yu Y, Zhang Y, Ye X, et al. Hypertension and breast cancer risk: a systematic review and meta-analysis. *Sci Rep.* 2017;7:44877.

22. Khalis M, Charbotel B, Chajès V, et al. Menstrual and reproductive factors and risk of breast cancer: A case-control study in the Fez region, Morocco. *PLoS One.* 2018;13(1):e0191333.

23. Lodha R, Joshi A, Paul D, Lodha KM, Nahar N, Shrivastava A, et al. Association between reproductive factors and breast cancer in an urban set up at central India: a case-control study. *Indian J Cancer.* 2011;48(3):303-307.

24. Anstey EH, Shoemaker ML, Barrera CM, et al. Breastfeeding and Breast Cancer Risk Reduction: Implications for Black Mothers, *Am J Prev Med.* 2017;53(3):S40-6.

25. John EM, Hines LM, Phipps AI, et al. Reproductive history, breast-feeding and risk of triple negative breast cancer: The Breast Cancer Etiology in Minorities (BEM) study. *Int J Cancer.* 2018;142(11):2273-2285.

26. Hildebrand JS, Gapstur SM, Campbell PT, et al. Recreational physical activity and leisure-time sitting in relation to postmenopausal breast cancer risk. *Cancer Epidemiol Biomarkers Prev.* 2013;22(10):1906-1912.

27. Loprinzi PD, Cardinal BJ, Smit E, Winters-Stone KM. Physical activity and breast cancer risk. *Journal of Exercise Science & Fitness.* 2012;10:1e7.

28. Szende B, Tyihák E. Effect of formaldehyde on cell proliferation and death. *Cell Biol Int.* 2010;34(12):1273-1282.

29. Noordiana N, Fatimah AB and Farhana YCB. Formaldehyde content and quality characteristics of selected fish and seafood from wet markets. *Int Food Res J.* 2011;18(1).