



Original article

Erythrocyte membrane saturated fatty acids profile in newly diagnosed Basal Cell Carcinoma patients



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SUMMARY

Background: Skin cancers are the most prevalent malignancy worldwide and Basal Cell Carcinoma (BCC) include the major type of nonmelanoma skin cancers. Fatty acids (FA) have a structural role in cell membranes and play an important role for many physiological and pathological immunologic pathways. Several prospective studies have been conducted on circulating fatty acids and the risk of prostate, breast and other cancers. The present study aimed to determine the saturated fatty acid composition differences of red blood cells (RBCs) in BCC patients and healthy control.

Methods: A hospital-based case-control study was conducted on new cases diagnosed of BCC patients. All subjects completed dietary recalls for dietary assessment. After fatty acids extraction, purification and preparation, gas chromatography was performed. The results were expressed in relative values (percent).

Results: Cases had lower RBC levels of Caproic acid (6:0) ($P < 0.001$), Caprylic acid (8:0) ($P = 0.01$), Capric acid (10:0) ($P = 0.01$), Palmitic acid (16:0) ($P = 0.02$) and higher RBC level of Pentadecanoic acid (15:0) ($P = 0.04$) and Stearic acid (18:0) ($P = 0.01$) compared with controls but did not differ in the level of the other primary saturated fatty acids. Saturation Index as defined by Stearic to Oleic acid ratio was significantly lower in BCC patients in comparison with Control group ($P = 0.02$).

Conclusion: Here we showed that BCC patient had considerable differences in the SFA profiles in comparison with healthy subjects.

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1. Introduction

Skin cancers are the most prevalent malignancy worldwide, with nonmelanoma skin cancers (NMSC) accounting for more than 30% of all cancers in the US. In Iran, skin cancer is the most common cancer with about 15% of all cancers. Basal cell (BCC) and squamous cell carcinomas (SCC) include the major types of NMSC. BCC is the common morphologic form of skin cancer in Iran. Although the

mortality rate of BCC is remarkably low, NMSC represents a significant health care burden and can cause major morbidity particularly as most NMSCs occur on highly visible areas such as the head and neck and face [1,2].

The major constitutional risk factors for all skin cancers seem to be skin color and the skin response to strong sunlight. Particularly in BCC development several factors have been suggested such as age, male sex, skin phototype (I, II), frequent sun exposure and sunburn, severe actinic damage, history of radiotherapy and etc. [3].

Although several animal studies show that high level of dietary fat intake decrease the time between UV exposure and tumor appearance and influence the promotional stage of UV carcinogenesis, there have been few human studies [4]. An intervention study indicated that participants randomized to an isocaloric

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low-fat diet experience lower occurrence of actinic keratoses and nonmelanoma skin cancer [5]. Another human study also mentioned that participants consuming higher percentages of dietary energy from fat seemed at increased risk for skin SCC [6].

Fatty acids (FA) have a structural role in cell membranes, influencing their fluidity and membrane enzyme activities and play an important role for many physiological and pathological immunologic pathways [7]. The possible influence of lipids on neoplastic development could be attributable to influence on the metabolism of neoplastic cells (proliferation and incorporation in the membranes of neoplastic cells), the function of lipids as intercellular messengers, or as mediators of the inflammatory reaction [8]. Also *In vitro* and *in vivo* studies show different effects of individual fatty acids on expression of genes concerned in multiple biologic pathways, comprising inflammation, lipid metabolism, and oxidative stress [9].

Several prospective studies have been conducted on circulating fatty acids and the risk of prostate, breast and other cancers [10,11]. A meta-analysis published in 2004 [11] indicated that oleic acid and the saturated palmitic acid were associated with increased breast cancer risk. Also reduction of saturation index as defined by the ratio of stearic acid (the most common saturated fatty acid [SFA]) to oleic acid (the most common monounsaturated fatty acid [MUFA]) has been observed in colorectal cancer, bronchogenic carcinoma, lymphoma, leukemia, malignant liver neoplasms and gallbladder cancer [12].

Studies suggest that the composition of human erythrocyte membrane fatty acid, other than dietary macronutrient intake and the interactions between dietary intake and endocrine changes may reflect fatty acid composition in other body tissues and are suitable for exploring the relations of the patterns of fatty acid metabolism to skin cancer risk [4,9].

In the current study, we explore the fatty acid composition of red blood cells (RBCs) to address individual fatty acid concentrations and possible differences between BCC patients and healthy control.

2. Methods and materials

2.1. Study design, participants and data collection

A hospital-based case-control study was conducted on new cases diagnosed of BCC patients in Razi hospital, Tehran, Iran. Cases were eligible if they had a histopathologically confirmed BCC diagnosis in Razi hospital in contact time, without a previous history of any cancers. The control subjects were randomly selected from first-visit outpatients who visited Razi Hospital. Control subjects were eligible if they had no prior history of skin cancer and were within the age, gender, and ethnicity grouping. There was no relation between diseases of controls and exposures studied. No study participant took drugs known to affect lipid metabolism or hormone replacement therapy. Also other diseases like diabetes mellitus, cardio vascular diseases and hypertension were excluded. For controlling confounding factors, case and control groups were matched on age, and Body Mass Index. All patients gave their informed consent to participate in the study, which was approved by the ethical committee of TUMS and performed in accordance with the guidelines in the Helsinki Declaration. Trained interviewers systematically collect and check information from the questionnaire and contacted the participants to describe the study and invite them, and scheduled the interview for dietary recalls and other questions. Two 24-h dietary recalls by nutritionist help were completed in randomly selected days (week day) and then analyzed by Nutritionist IV software (First Databank, San Bruno, CA, USA) adjusted for Iranian foods. Body weight was measured

without shoes and in a minimum clothes condition by the use of a digital scale (Seca, Hamburg, Germany) to the nearest 0.1 kg. Height was calculated to the nearest 0.1 cm by using an inelastic tape measure (Seca, Hamburg, Germany). BMI was calculated as weight in kg divided by height in meters squared. Five millimeters of blood samples from vein were collected after 8–12 h fasting. We used serum for lipid profile (triglyceride, total cholesterol, HDL cholesterol and LDL cholesterol) (Pars Azmoon kit, Iran).

2.2. Sample size calculation

To measure the sample size, based on type one (α) and type two errors (β) as 0.05 and 0.20 (power = 80%), respectively and according to the previous study [9], we considered 1.04 as standard deviation (SD) and 0.78 as the difference in mean or effect size (d) of fatty acids in RBC membrane as the key variable. Therefore, we needed 28 subjects in each group. Eventually we recruited 40 patients per group to consider the possible dropouts. From April 2010 to February 2013 in 3 year-duration, 80 participants were interviewed for the study, 40 cases and 40 controls.

3. Reagents and standards

Analytical grade chloroform, methanol and n-hexane were obtained from Merck (Darmstadt, Germany). BF3 14%, sodium sulfates and sodium chloride standards were acquired from Sigma–Aldrich (St. Louis, USA). 37 FAME Mix standard, were purchased from Supelco, Pennsylvania, USA. Water (18.2 M, TOC < 5 ppm) was purified and filtered through a Milli-Q Plus system filter (Millipore, Bedford, USA).

3.1. Fatty acids extraction, purification and preparation of fatty acid methyl esters

Ten milliliters of fasting venous blood were collected from each patient in an EDTA bottle and centrifuged at 1500 Rpm for 5 min to separate the erythrocytes. The plasma was recorded for lipid profile analysis and the erythrocytes were washed three times with phosphate buffered saline (PBS) to exclude iron of hemoglobin for preventing oxidative degradation of fatty acids. All RBCs were reserved in 500 μ L micro tubes in -80 °C for gas chromatography measurement. Each sample of red blood cells (RBC) was thawed to room temperature. The lipids were extracted from the erythrocytes with 2:1 (v/v) chloroform–methanol using the Folch et al. (1957) procedure [13] and centrifuged at $1500 \times g$ for 10 min. Preparation of fatty acid methyl esters was carried out by of BF3·MeOH 14%. So, 200 μ L of dried RBC samples (Samples dried by nitrogen gas in order to evaporate water for better fatty acid methylation), 2 μ L BF3·MeOH 14% and 1 μ L methanol incubated for 10 min at 60 °C [14]. To the samples were added 2 ml of N-hexane solution and they were stirred for 10 min by Vortex. The upper layer was recorded, drown off into a vial.

3.2. Gas chromatography and fatty acids quantification

Gas chromatography analyses were performed by a 6500GC YoungLin (Korea) instrument with auto-sampler, a split/splitless injector, FID detector and a hydrogen gas generator. Separation of FAME (fatty acids methyl ester) was carried-out on a TR-CN100 column (Teknokroma, 37 FAMEMIX-MS detector, 60 m \times 0.25 mm \times 0.20 μ L, Standard: 1 μ L FAME MIX in methylene chloride, Injection: 280 °C, split 20:1). Hydrogen was used as carrier gas, constant flow mode; the amount injected was 1 μ L in splitless mode and 24 PSI. The temperature of the injector and the FID detector were 280 °C. Inlet temperature 240 °C, split 40:1, injection

0.20 µl. The initial temperature of the oven was 90 °C, for 5 min, then to 220 °C at 4 °C min⁻¹ for another 5 min, and finally the temperature increased to 240 °C: 4 °C/min for total of 47.5 min. Quantification of the methyl esters of fatty acids extracted was done by the use of a mixture of the above-mentioned standards. For calibration we used Fatty acid standard (Supelco, USA) which has 37 fatty acids in 2%, 4% and 6%. Four solutions of increasing concentration (0.3, 0.2, 0.1, 0.05 ppm) of the mix of standards (Teknokroma) were prepared; each solution was analyzed three times and the resulting chromatograms were used to make the calibration curve for each component of the mixture. This gives a computer printout, could completely objective means of calculating the percentage of every fatty acid in sample. The various peaks represent different fatty acids. The computer was planned to measure the area under every peak. The percentage of each fatty acid present was revealed from the percentage of each peak area compared to the total peak area. The results were analyzed using Excel and expressed in relative values (percentages).

4. Data analysis

All values expressed as mean ± SEMs. To compare categorical variables, the Pearson chi-square test was used. Continuous variable and dietary intakes difference between case and control groups assessed by Independent T test and distribution of variables was assessed by Kolmogorov–Smirnov test. $P < 0.05$ was considered as statistically significant. All statistical analyses were done using the Statistical Package for Social Science version 17 (SPSS Inc., Chicago, Illinois, USA).

5. Results

The mean ages of the enrolled BCC patients and control group were 57.76 ± 1.56 and 54.05 ± 1.16 years, respectively. There was no statistically significant difference for any of the demographic or medical history between those case and control groups. Table 1 shows demographic characteristics and of healthy people and BCC groups.

Table 2 presents that intakes of energy are similar in BCC and healthy groups. Macro nutrients like total fat, protein and carbohydrate had not differences between the two groups. Some micronutrients (selenium, copper, zinc beta carotene, α -tocopherol, beta-carotene and molybdenum) were not different in patients and healthy groups. Various types of fats were presented in Table 2 and there is not any difference between BCC and type of fat intake.

Table 3 presents comparison of lipid profile such a triglyceride, total cholesterol, HDL cholesterol and LDL cholesterol between the two groups. There were not statistically significant differences between subjects in two groups in lipid profiles.

Table 4 displays percent of every saturated fatty acid from total fatty acids of red blood cell membranes for BCC and healthy people.

Table 1

Demographic characteristics and medical history of healthy and Basal Cell Carcinoma group.^a

Demographic characteristics		BCC	Control	P-value*
Sex	Male (%)	28 (70%)	21 (52.5%)	0.18**
	Female (%)	12 (30%)	19 (47.5%)	
Age (years)		57.76 ± 1.56	54.05 ± 1.16	0.06*
Weight (kg)		72.39 ± 1.94	72.48 ± 2.46	0.98*
Height (cm)		167.76 ± 1.59	166.30 ± 1.36	0.49*
BMI (kg/m ²)		26.02 ± 0.74	25.74 ± 0.67	0.78*

*P-value reported based on Independent Sample T-Test.

**P-value reported based on Chi-Square test.

^a Mean ± SE.

Table 2

Energy, macronutrients and micronutrients intakes of BCC subjects and control group.^a

	BCC	Control	P-value*
Total energy (kcal)	2537.65 ± 146.68	2246.55 ± 234.98	0.27
Total carbohydrate (g)	327.32 ± 23.78	320 ± 27.55	0.86
Total protein (g)	68.85 ± 3.33	68.90 ± 4.99	0.99
Total fat(g)	80.82 ± 6.02	85.49 ± 8.09	0.65
SFA (g)	20.22 ± 1.91	17.57 ± 1.55	0.36
MUFA (g)	32.00 ± 3.98	29.63 ± 2.84	0.62
PUFA(g)	30.41 ± 3.36	36.06 ± 6.39	0.39
Cholesterol (mg)	115.37 ± 39.94	120.42 ± 11.65	0.74
Oleic fat (g)	19.56 ± 2.06	23.24 ± 2.2	0.26
Linolenic (g)	2.47 ± 1.33	1.33 ± 0.39	0.54
Linoleic (g)	28.47 ± 3.19	34.27 ± 21.18	0.37
DHA (g)	0.02 ± 0.01	0.001 ± 0.00	0.39
EPA (g)	0.01 ± 0.00	0.00 ± 0.00	0.43
Molybdenum (µg)	46.56 ± 13.60	41.49 ± 10.03	0.80
Selenium (mg)	0.22 ± 0.15	0.04 ± 0.00	0.38
Chromium (mg)	0.05 ± 0.00	0.03 ± 0.00	0.11
Copper (mg)	1.40 ± 0.20	1.20 ± 0.15	0.49
Zinc (mg)	8.38 ± 0.53	9.27 ± 0.81	0.34
Alpha tocopherol (mg)	12.63 ± 1.60	14.36 ± 2.86	0.57
Beta carotene (µg)	613.55 ± 186.05	538.35 ± 220.61	0.80

*P-value reported based on Independent Sample T-Test.

SFAs = saturated fatty acids, PUFAs = polyunsaturated fatty acids, MUFAs = monounsaturated fatty acids.

^a Mean ± SE.

Table 3

Serum lipid in patients and healthy people.^a

Serum lipid	BCC	control	P-value*
Triglyceride(mg/dl)	138.37 ± 6.57	116 ± 6.57	0.56
TC (mg/dl)	174 ± 5.32	159.54 ± 6.35	0.81
LDL-c(mg/dl)	98.84 ± 3.91	88.67 ± 3.97	0.37
HDL-c(mg/dl)	36.05 ± 0.98	37.54 ± 1.34	0.72

*P-value reported based on Independent Sample T-Test.

TC; Total cholesterol, LDL-c; Low density lipoprotein cholesterol, HDL-c; High density lipoprotein cholesterol.

^a Mean ± SE.

Cases had lower RBC levels of Caproic acid (6:0) ($P < 0.001$), Caprylic acid (8:0) ($P = 0.01$), Capric acid (10:0) ($P = 0.01$), Palmitic acid (16:0) ($P = 0.02$) and higher RBC level of Pentadecanoic acid (15:0) ($P = 0.04$) and Stearic acid (18:0) ($P = 0.01$) compared with controls but did not differ in the level of the other primary saturated fatty acids Undecylic acid (C11:0), Tridecylic acid(C 13:0), Myristic acid(C14:0), Margaric acid (C 17:0), Arachidic acid (C 20:0), Heneicosylic acid (C 21:0), Behenic acid (C 22:0), Tricosylic acid (C 23:0) and Lignoceric acid (C 24:0). It must be mentioned that we were not able to detect Lauric acid for BCC patients as shown in Table 4. Saturation Index as defined by Stearic to Oleic acid ratio was significantly lower in BCC patients in comparison with Control group ($P = 0.02$).

6. Discussion

The most significant finding of this study was that percentages of erythrocyte membrane fatty acids differed in patients with incident BCC cancer in comparison with individuals with no malignant diseases. Our results indicated that BCC patients had lower RBC levels of Caproic acid (6:0) ($P < 0.001$), Caprylic acid (8:0) ($P = 0.01$), Capric Acid (10:0) ($P = 0.01$), Palmitic acid (16:0) ($P = 0.02$) and higher level RBC level of Pentadecanoic acid (15:0) ($P = 0.04$) and Stearic acid (18:0) ($P = 0.01$) compared with controls. Furthermore, individuals with a first skin BCC had a decreased ratio of stearic acid to oleic acid in erythrocyte membranes compared with controls.

Table 4
Saturated fatty acid of red blood cell membrane in BCC subjects and control group.^a

Saturated fatty acids	BCC	Healthy	P-value ^b
C 6:0 (%)	0.00 ± 0.00	0.03 ± 0.01	<0.001*
C 8:0 (%)	0.01 ± 0.00	0.02 ± 0.00	0.01*
C 10:0 (%)	0.02 ± 0.00	0.04 ± 0.00	0.01*
C 11:0 (%)	0.03 ± 0.01	0.04 ± 0.01	0.24
C 12:0 (%)	0	0.01 ± 0.00	–
C 13:0 (%)	0.03 ± 0.01	0.03 ± 0.01	0.79
C 14:0 (%)	0.03 ± 0.01	0.04 ± 0.01	0.82
C 15:0 (%)	0.05 ± 0.01	0.02 ± 0.01	0.04*
C 16:0 (%)	0.08 ± 0.01	0.11 ± 0.01	0.02*
C 17:0 (%)	0.03 ± 0.01	0.03 ± 0.01	0.98
C 18:0 (%)	0.20 ± 0.02	0.14 ± 0.00	0.01*
C 20:0 (%)	0.03 ± 0.01	0.02 ± 0.00	0.44
C 21:0 (%)	0.04 ± 0.01	0.02 ± 0.00	0.09
C 22:0 (%)	0.21 ± 0.20	0.00 ± 0.00	0.41
C 23:0 (%)	0.03 ± 0.01	0.02 ± 0.02	0.83
C 24:0 (%)	0.02 ± 0.01	0.01 ± 0.00	0.34
SI	0.57 ± 0.07	0.79 ± 0.06	0.02*

Saturation index.

*Statistically significant difference.

^a Mean ± SE.

^b Independent Sample T-Test.

Also no major differences were observed in anthropometric parameters, dietary intake and lipid profile in BCC patients compared with values for control patients with no malignant diseases.

One possible explanation for these results could be modifications in the metabolism of fatty acids in cancer patients. The associations of RBC membrane fatty acid profile with BCC of the skin are consistent with animal studies [4]. UV radiation reduces cell-mediated immunity by increasing suppressor T cells. Sunburn is the inflammatory response of cells to UV-B induced damage [15]. Rodent models of photocarcinogenesis of skin cancer give some of the earliest evidence that dietary fat acts as a tumor promoter [4] with higher levels cause increases in tumor incidence [4]. Specific types of fat exert differential carcinogenic effects in rodent models [4], dietary fat composition adjusts cellular immunity affecting cell membrane fluidity and integrity, which in turn alters inflammatory response [15].

On the contrary of self-report methods, e.g., food-frequency questionnaires (FFQs) and diet records, biomarkers of dietary fatty acids have unique strengths [16]. Biomarkers do not rely on the precision of memories, alertness of fat intake, or readiness to report details of diet [16]. Because of limitation in the availability of adipose tissue [17] for long term integrated dietary intake, individual metabolism, and physical activity, suggestive alternative like blood specimens are more available and widely used. Because turnover of blood cells is more rapid in comparison with adipose tissue and also erythrocyte membrane content reflects dietary lipid intake along with endogenous lipid biosynthesis, also it has been discussed that these membranes should be better indicator of nutritional status and functional energy requirement compared with adipose tissue [18,19]. Overall, studies showed that correlations with intake were stronger for erythrocytes than for plasma [18].

Most human diets contain a variety of saturated fatty acids of different chain lengths. The major saturated fatty acid in the diet is palmitic acid (C16:0), followed by stearic acid (C18:0). Rich sources of Palmitic acid is palm oil and in butter, milk, cheese, and meats [20]. In the current study, skin cancer patients were associated with increasing levels of palmitic acid in erythrocyte membranes. In comparison with the traditional eastern diet, meat consumption has extremely increased since 1950 [21]. The ratios of processed meat/fish are 1.3 for energy and 2.2 for fat intake, perhaps increasing the chance of cancer development [21]. In,

Mediterranean, and American diets, the amount of fat intake (energy intake, %) and the ratios of SFAs:MUFAs:PUFAs are 70–80 g (30–35%) and 2:5:2, and 80–90 g (35–40%) and 2:2:1, in that order, and this diversity may be directly related to their disease prevalence, including cancers in several sites [21]. Also it must be noted that the lipid composition of erythrocyte membranes is more than a direct reflection of dietary fatty acid intake [22]. Saturated fatty acids could be endogenously synthesized from carbohydrates. This membrane property is eminent and shown in studies [22]. A fat-free, carbohydrate rich diet fed to adult subjects for 4–11 weeks resulted in a significant increase in C16:0, C16:1, C18:0, and C18:1, the fatty acid products of lipogenesis [22]. On the other hand if intake of carbohydrate is very high and the intake of fat is very low, the liver rapidly converts carbohydrate into fatty acids, so the important point is that membrane lipids are a sign of the balance of dietary carbohydrates and fats [4,22].

SFAs, and notably long-chain SFAs, have been associated with inflammation. One systematic review pointed to a potential positive relationship between SFA and C-reactive protein (CRP) [23]. Although the mechanism is blurred, toll-like receptor (TLR) 4, TLR2, the synthesis of ceramides, the formation of lipid rafts and fetuin seem to be implicated. On the other hand, medium-chain SFAs have shown beneficial health effects including suppression of body fat accumulation [24] In our study, long chain SFA was significantly higher in the RBC membranes of patients with BCC than in healthy people and short chain SFA was lower in BCC patients. These results are consistent with other studies in other cancers. Similar results also duplicated in SCC [4], colon [25], breast [10] and Multiple myeloma [8].

Most of the oleic acid in mammalian tissue is derived from the saturated stearic acid residue. Stearic acid is converted into oleic acid by the liver microsomal desaturase system (D9 desaturase). Increased D9 desaturation and low saturation index (SI) have been scrutinized in colorectal and bronchogenic carcinoma, lymphoma, leukemia and malignant liver neoplasms [8]. Also, a reduction in the SI of erythrocytes in patients with leukemia has been identified [26]. Pandey et al. described that the decrease in SI is not type-specific but is associated with neoplasia in general [8]. High levels of MUFAs are required by mouse mammary carcinoma cells and the required MUFA levels are guaranteed by overexpression of the genes encoding $\Delta 9$ -desaturase. Inhibition of $\Delta 9$ -desaturase and, as a result, of oleic acid biosynthesis inhibits the growth of transplanted mammary tumor in rats [25]. Our finding of a low-erythrocyte-membrane SI in BCC patients is consistent with the results of other studies. These findings show that, rather than the individual components, the ratio between the two fatty acids may be more frankly related to cancer. A diet high in MUFAs, which are extensively synthesized endogenously, is probably one determinant of erythrocyte membrane MUFAs. Therefore, the relationship of high levels of membrane oleic acid and low SI might be related to factors other than diet. Several studies have suggested a link between $\Delta 9$ -desaturase activity and tumor growth [25]. The fat content of the diet has an important effect on $\Delta 9$ -desaturase activity. High levels of SFAs increase $\Delta 9$ -desaturase activity by twofold to threefold, whereas PUFAs decrease it [25]; as a result, high levels of oleic acid and low SI in tissues may be because of a diet poor in PUFAs. A correlation study on one cohort, provided a negative correlation ($r = -0.25$; $P = 0.009$) between erythrocyte membrane oleic acid and dietary PUFAs. A high-cholesterol diet also seems to increase $\Delta 9$ -desaturase activity, resulting in increased mono-unsaturation of the membrane fatty acids in rat liver. $\Delta 9$ -desaturase is activated by carbohydrate administration, and it is well established that insulin enhances $\Delta 9$ -desaturase activity. The possible relationships among dietary carbohydrate, insulin resistance, and cancer risk are receiving increasing attention [25].

7. Conclusion

The current study provides further evidence that fatty acids, in particular, maybe have critical role in human skin cancer. In conclusion, here for the first time we showed that BCC patient had considerable differences in the SFA profiles in comparison with healthy patients. Our finding was consistent with other studies in other cancers. We explore the exact cause of these abnormalities and we seek dietary factors. The erythrocyte content of SFA seems to be influenced by the fatty acid composition of the diet and by the endogenous synthesis and metabolism, in which dietary and other factors may mediate in ways that are partly revealed. Dietary modification earns considerable attention and clarification in all diseases and also cancer. Obviously, further studies are required to clarify these intriguing aspects of the relationship between red blood cell membrane fatty acid composition and skin cancer pathogenesis.

Ethical considerations

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors.

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Authors' contribution

FR, AHE, AE, MHJ, EG, and MZ performed the research and contributions to design of the study. EG prepared the primary draft. HM; contribution to data analysis; MHJ and MJ; edited the final draft and final approval of the manuscript.

Conflict of interest

The authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.clnesp.2017.11.007>.

References

- [1] Keyghobadi N, Rafiemanesh H, Mohammadian-Hafshejani A, Enayatrad M, Salehiniya H. Epidemiology and trend of cancers in the province of Kerman: southeast of Iran. *Asian Pac J Cancer Prev* 2015;16(4):1409–13.

- [2] Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. *Br J Dermatol* 2012;166(5):1069–80.
- [3] Hallaji Z, Rahimi H, Mirshams-Shahshahani M. Comparison of risk factors of single Basal cell carcinoma with multiple basal cell carcinomas. *Indian J Dermatol* 2011;56(4):398.
- [4] Harris RB, Foote JA, Hakim IA, Bronson DL, Alberts DS. Fatty acid composition of red blood cell membranes and risk of squamous cell carcinoma of the skin. *Cancer Epidemiol Prev Biomark* 2005;14(4):906–12.
- [5] Black HS. Influence of dietary factors on actinically-induced skin cancer. *Mutat Res/Fundam Mol Mech Mutagen* 1998;422(1):185–90.
- [6] Hakim IA, Harris RB, Ritenbaugh C. Fat intake and risk of squamous cell carcinoma of the skin. *Nutr Cancer* 2000;36(2):155–62.
- [7] Coviello G, Tutino V, Notarnicola M, Caruso MG. Erythrocyte membrane fatty acids profile in colorectal cancer patients: a preliminary study. *Anticancer Res* 2014;34(9):4775–9.
- [8] Jurczyszyn A, Czepiel J, Gdula-Argasińska J, Czapkiewicz A, Biesiada G, Drózd M, et al. Erythrocyte membrane fatty acids in multiple myeloma patients. *Leuk Res* 2014;38(10):1260–5.
- [9] Shannon J, King IB, Moshofsky R, Lampe JW, Gao DL, Ray RM, et al. Erythrocyte fatty acids and breast cancer risk: a case-control study in Shanghai, China. *Am J Clin Nutr* 2007;85(4):1090–7.
- [10] Pouchieu C, Chajès V, Laporte F, Kesse-Guyot E, Galan P, Hercberg S, et al. Prospective associations between plasma saturated, monounsaturated and polyunsaturated fatty acids and overall and breast cancer risk—modulation by antioxidants: a nested case-control study. *PLoS One* 2014;9(2):e90442.
- [11] Saadatian-Elahi M, Norat T, Goudable J, Riboli E. Biomarkers of dietary fatty acid intake and the risk of breast cancer: a meta-analysis. *Int J Cancer* 2004;111(4):584–91.
- [12] Pandey M, Sharma LB, Singh S, Shukla VK. Erythrocyte membrane fatty acid profile and saturation index in gallbladder carcinogenesis: a case-control study. *World J Surg Oncol* 2003;1(1):5.
- [13] Folch J, Lees M, Sloane-Stanley G. A simple method for the isolation and purification of total lipids from animal tissues. *J Biol Chem* 1957;226(1):497–509.
- [14] Metcalfe L, Schmitz A. The rapid preparation of fatty acid esters for gas chromatographic analysis. *Anal Chem* 1961;33:363–4.
- [15] Cope RB, Bosnic M, Boehm-Wilcox C. Dietary butter protects against ultraviolet radiation-induced suppression of contact hypersensitivity in Skh: HR-1 hairless mice. *J Nutr* 1996;126(3):681.
- [16] Cantwell MM. Assessment of individual fatty acid intake. *Proc Nutr Soc* 2000;59(02):187–91.
- [17] Baylin A, Campos H. The use of fatty acid biomarkers to reflect dietary intake. *Curr Opin Lipidol* 2006;17(1):22–7.
- [18] Sun Q, Ma J, Campos H, Hankinson SE, Hu FB. Comparison between plasma and erythrocyte fatty acid content as biomarkers of fatty acid intake in US women. *Am J Clin Nutr* 2007;86(1):74–81.
- [19] Jackson JA, Riordan HD, Hunninghake R, Meng X, Sarwar Y. Red blood cell membrane fatty acids as a diagnostic test. *J Oithomolec Mad* 1997;12:20–2.
- [20] Bartsch H, Nair J, Owen RW. Dietary polyunsaturated fatty acids and cancers of the breast and colorectum: emerging evidence for their role as risk modifiers. *Carcinogenesis* 1999;20(12):2209–18.
- [21] Kuriki K, Wakai K, Hirose K, Matsuo K, Ito H, Suzuki T, et al. Risk of colorectal cancer is linked to erythrocyte compositions of fatty acids as biomarkers for dietary intakes of fish, fat, and fatty acids. *Cancer Epidemiol Prev Biomark* 2006;15(10):1791–8.
- [22] Farquhar JW, Ahrens Jr EH. Effects of dietary fats on human erythrocyte fatty acid patterns. *J Clin Investig* 1963;42(5):675.
- [23] Mu L, Mukamal KJ, Naqvi AZ. Erythrocyte saturated fatty acids and systemic inflammation in adults. *Nutrition* 2014;30(11):1404–8.
- [24] Ruiz-Núñez B, Kuipers RS, Luxwolda MF, De Graaf DJ, Breeuwsma BB, Dijk-Brouwer DJ, et al. Saturated fatty acid (SFA) status and SFA intake exhibit different relations with serum total cholesterol and lipoprotein cholesterol: a mechanistic explanation centered around lifestyle-induced low-grade inflammation. *J Nutr Biochem* 2014;25(3):304–12.
- [25] Pala V, Krogh V, Muti P, Chajès V, Riboli E, Micheli A, et al. Erythrocyte membrane fatty acids and subsequent breast cancer: a prospective Italian study. *J Natl Cancer Inst* 2001;93(14):1088–95.
- [26] Pandey M, Khatri AK, Dubey S, Gautam A, Shukla VK. Erythrocyte membrane stearic to oleic acid ratio in carcinoma of the gallbladder: a preliminary study. *Eur J Surg Oncol (EJSO)* 1998;24(1):43–6.