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ORIGINAL ARTICLE

Radiation interaction parameters for blood samples of breast cancer patients: an MCNP study

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Abstract
The main goal of this study was to determine radiation interaction parameters such as mass attenuation coefficients, effective atomic numbers, and effective electron densities depending on element concentrations (Na, K, Cu, Zn, Al, Ca, Mg Cr, Fe, Se) in blood samples of patients with breast cancer. Eighty blood samples were collected and analyzed in this study (40 from breast cancer patients and 40 from healthy patients). The determination of element concentrations of the samples was performed with inductively coupled plasma-mass spectrometry (ICP-MS) and inductively coupled plasma-optical emission spectrometry (ICP-OES) after which the element concentrations were normalized to percentage. Mass attenuation coefficients were calculated by Monte Carlo simulation method. In addition, effective atomic numbers and effective electron density values of the blood samples were calculated with the ZXCOM program. One of the most important results of this study is that differences in radiation interaction parameters between the two groups were observed. More specifically, the mass attenuation coefficients of the healthy group's blood samples were higher than those of the cancerous group at photon energies of 50 keV, 100 keV, 250 keV and 500 keV, while they were lower at 1 MeV. All the MCNP results were consistent with the results obtained from ZXCOM. As the main result of this study it is concluded that photon atomic parameters such as mass attenuation coefficient, effective atomic number and electron density may be considered in cancer diagnosis or treatment modalities.

Keywords Breast cancer · Monte Carlo · MCNP · Mass attenuation coefficient · Electron density

Introduction

Cancer is at the forefront of death causes in economically developed countries and the second most common cause of death in developing countries (World Health Organization 2008). According to Globocan (2012), the global average of breast cancer incidence and mortality cases per 100,000 women are 43.3 and 12.9, respectively (Ferlay et al. 2015; Globocan 2012). For many years and despite of considerable efforts, however, breast cancer is still the most common type of cancer in women. About 23% of cancer cases recorded worldwide are breast cancer cases (Aristizábal-Pachón et al. 2015; Ferlay et al. 2015) with increasing tendency. This increment can for example be attributed to improvements in breast cancer diagnosis (Ozmen 2014). About 45% of women diagnosed with cancer are in the age range from 50 to 69 years, and 40% are in the age range from 25 to 49 years (Khoshbin et al. 2015).

It is known that there are various factors that cause cancer, among those might be the excess or deficiency of some chemical elements in the human body. In fact, various diseases are related to the amount of certain elements in the body (Neelamegam et al. 2011; Al Faris and Ahmad 2011). Such elements are important for the stability of the metabolism. For example the excess of certain trace

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elements may cause problems in the body including negative effects on metabolic functions (Stanislas et al. 2019).

More specifically, imbalance in concentrations of certain elements may affect the cycle of biological processes and are associated with many diseases such as neurological disorders, cancer, renal failure and autoimmune disease (Mizuno et al. 2014; Shokrzadeh et al. 2009; Wach et al. 2018). By determining these elemental imbalances, diagnostic or treatment modalities can be developed. There are various studies showing a strong relation between chemical element concentrations in the human body and cancer (Gecit et al. 2011; Cobanoglu et al. 2010; Mohammadi et al. 2014). While certain elements are indispensable for biological structures of the human body, they may be toxic if they are too concentrated (Gecit et al. 2011).

Physical parameters describing the interaction of radiation with matter, such as mass attenuation coefficients (μ_m), effective atomic numbers (Z_{eff}) and effective electron densities (N_{el}), are directly related to the elements in the investigated material. That is, μ_m, Z_{eff} and N_{el} for tissue, which vary depending on the concentration of the elements in that tissue, may be a marker for many diseases. Indeed, many studies with respect to tissue/blood showed that there is a correlation between several cancer diseases and electron density values (Antoniassi et al. 2010, 2011; Bursalıoglu et al. 2017). For example, in a study by Antoniassi et al. electron densities in normal (fibroglandular and adipose) and neoplastic (benign and malignant) human breast tissue were determined by the Compton scattering technique, and it was reported that malignant tissue showed the highest electron density while adipose showed the lowest (Antoniassi et al. 2010, 2011). Additionally, there was a similar study about electron density and thyroid cancer (Bursalıoglu et al. 2017). This study showed that electron density values were higher in human blood serums from radioiodine therapy patients as compared electron density values in comparable samples from a healthy group. This was confirmed by Ohira and co-workers (Ohira et al. 2018).

Although it is known that radiation attenuation depends on elemental concentrations (Monte Carlo Team 2003), there were only a few studies attempting to investigate the relationship between tissues and N_{el}, and the number of studies on N_{el} in blood is limited (Manjunatha and Rudraswamy 2012, 2013). Indeed there were several studies that quantified the relationship between the concentration of trace elements in the blood of patients suffering from various cancer types (Platz et al. 2002; Cabré et al. 2018; Topdagi et al. 2018; Toker et al. 2019). See Silvera and Rohan (2007) for a comprehensive review. However, to the best of the authors' knowledge no studies have been published so far on the relationship between breast cancer and control groups in terms of radiation interaction parameters in blood.

Consequently, in the present study the feasibility of μ_m, Z_{eff} and N_{el} in blood as markers for breast cancer was evaluated. The main goal was to investigate any relation between breast cancer and μ_m, Z_{eff} and N_{el} of blood. Firstly, element concentrations in blood samples of breast cancer patients were determined with inductively coupled plasma-mass spectrometry (ICP-MS) and inductively coupled plasma-optical emission spectrometry (ICP-OES). Concentrations of trace elements (aluminum, chromium, iron, copper, zinc, selenium) were determined by ICP-MS, while those of macro-elements (sodium, potassium, magnesium, calcium) were determined by ICP-OES. After that, the Z_{eff} and N_{el} values of the blood samples were determined by the ZXCOM program, and μ_m values were calculated with the Monte Carlo code MCNP for different photon energies (50 keV, 100 keV, 250 keV, 500 keV and 1 MeV). Then any relationship between μ_m, Z_{eff} and N_{el}, and breast cancer disease was investigated. This initiative describes an entirely new approach and, consequently, adds novel data to the literature which currently includes only insufficient information on this relation.

Materials and methods

Collection of blood samples

The use of blood samples from cancer patients for the molecular analyses described here was conducted according to the standards set by the ethical committee of the Atatürk University and, accordingly, approved by the institutional ethical review board. Eighty samples were collected randomly from samples registered by the Medical Oncology Policlinic of the Department of Internal Medicine in Ataturk Medical Faculty. Blood samples were collected from two different groups (i.e., from 40 breast cancer patients and 40 healthy individuals).

Determination of element concentrations

Element concentrations in the blood samples were determined using ICP-MS (Agilent 7700 series) and ICP-OES (ICPE-9000, Shimadzu) located at the Central Laboratory of Yildiz Technical University. More specifically, trace elements such as aluminum, chromium, iron, copper, zinc, and selenium were measured with ICP-MS, while sodium, potassium, magnesium and calcium were measured with ICP-OES. In both methods, external calibration curves were used in the calculation of elemental concentrations. In ICP-MS, at least two ions were quantified to make sure that there is no interference between analyte signals. Three replicate measurements were performed for each sample and relative standard deviation values for the replicates of each analyte were found to be lower than 10%. All chemicals used for sample preparation were of analytical grade. Sample preparation was carried out on a clean bench to avoid contamination from ambient dust and air.

Z_{eff} and N_{el} via ZXCOM

Electron density (N_{el}) can be determined with different methods. One of these methods is to calculate electron density is based on the effective atomic number (Z_{eff}). This process includes three phases: (a) measurement of the element concentration in the material of interest; (b) calculation of Z_{eff} using these element concentrations and, (c) calculating N_{el} of the samples by using Z_{eff} (Eyecioglu et al. 2016).

In the present study, electron densities were calculated with the ZXCOM software which offers one of the numerical methods available for this purpose, because it allows for a rapid calculation of both N_{el} and Z_{eff} for photon energies from 1 keV to 100 GeV, for any material (provided the element concentration in the material of interest is known) (Eyecioglu et al. 2016).

Briefly, ZXCOM is a program that simulates an experimental geometry where the energy of the radiation source can be selected from 1 keV to 100 GeV. Also, any element, compound or mixture of those can be used as a sample material. The effective atomic number and electron density of the sample can then be determined by taking into account the radiation interactions with matter as a result of this experimental geometry (Eyecioglu et al. 2017; Nuroglu et al. 2016).

Calculation of mass attenuation coefficients with MCNP

In general, Monte Carlo simulation is one of the most effective tools used to analyze the interaction of radiation with matter (Khan and Gibbons 2014). Programs such as MCNP and Geant4, among others, are the most commonly used programs in Monte Carlo calculations. In the present study, MCNP version 5 was used.

The geometry implemented in MCNP for the present study is shown in Fig. 1. A working space of 80 cm diameter was created in the input file for this geometry. A point radiation source (diameter: 2 mm) was formed within the working space and the sample was placed at a distance of 1 cm from the source. In the same direction, a lead collimator with a diameter of 6 cm was placed at a distance of 35 cm. A sodium iodide (NaI) detector was placed 4 cm inside the collimator. The detector had a width of 2 cm and a diameter of 4 cm. The detector was designated for calculation of average photon fluence (F4 tally in the MCNP-5 code).

The mass attenuation coefficient values of the samples were calculated by using the photon flux with the help of the transmission method. Photon energies of 50 keV, 100 keV, 250 keV, 500 keV and 1 MeV were chosen as radiation sources and 400 simulations were run for the samples from the 40 healthy individuals and 40 cancer patients. All simulations were run using an Intel® Core (TM) i5-3317u @ 1.70 GHz processor and each simulation was run with 10^8 histories.

Statistical analysis

To investigate the statistical significance of any differences between the two groups, the independent samples *t* test or Mann–Whitney *U* test can be applied according to the distribution of the data. The independent samples *t* test can be used when the data of different groups follow a normal distribution. However, the Mann–Whitney *U* test was chosen in the present work because not all data followed a normal distribution. These statistical procedures also included the widely known Kolmogorov–Smirnov test used to test for normality.

Results and discussion

The elemental compositions in the blood samples from the healthy individuals and cancer patients are given in Table 1. Tables 2and 3 show the descriptive statistics for the N_{el} and

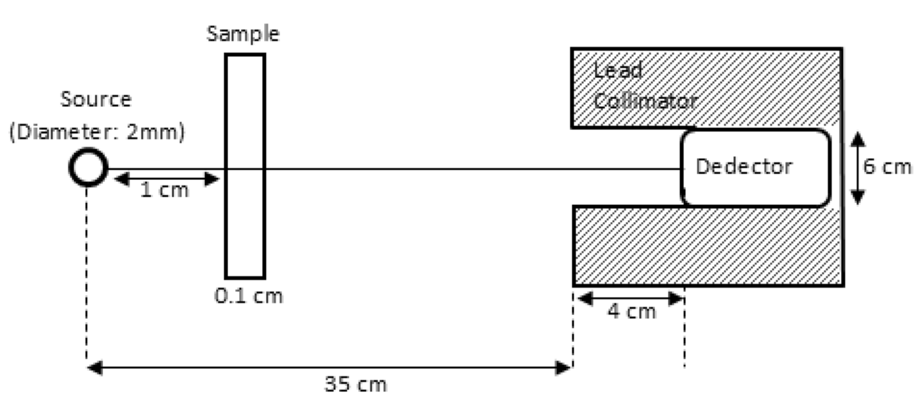

Fig. 1 Geometry implemented in MCNP

Table 1 The elemental composition of the blood samples from healthy individuals and breast cancer patients (SD: one-sigma standard deviation)

Element	Group	Mean ± SD
Al (ppb)	Healthy individuals	19.15 ± 11.63
	Breast cancer patients	11.10 ± 9.73
Ca (ppm)	Healthy individuals	100.29 ± 24.40
	Breast cancer patients	99.01 ± 31.19
Cr (ppb)[a]	Healthy individuals	22.19 ± 22.17
	Breast cancer patients	12.21 ± 26.74
Cu (ppb)	Healthy individuals	0.93 ± 0.21
	Breast cancer patients	1.17 ± 0.31
Fe (ppm)	Healthy individuals	352.41 ± 74.54
	Breast cancer patients	341.04 ± 115.14
K (ppm)[a]	Healthy individuals	994.67 ± 132.94
	Breast cancer patients	1018.28 ± 272.16
Mg (ppm)	Healthy individuals	33.60 ± 4.51
	Breast cancer patients	38.10 ± 9.69
Na (ppm)[a]	Healthy individuals	1505.25 ± 162.57
	Breast cancer patients	1591.98 ± 376.95
Se (ppb)[a]	Healthy individuals	91.68 ± 25.57
	Breast cancer patients	50.56 ± 12.06
Zn (ppm)[a]	Healthy individuals	4.49 ± 0.80
	Breast cancer patients	4.48 ± 1.60

[a]Toker et al. (2019)

Table 2 N_{el} descriptive statistics for the two groups of healthy individuals and cancer patients

Group	Mean ($\times 10^{23}$)	SD ($\times 10^{21}$)	Mean rank*
50 keV			
Healthy individuals	3.13	6.82	45.04
Breast cancer patients	3.11	7.99	35.96
100 keV			
Healthy individuals	3.06	3.81	44.86
Breast cancer patients	3.05	4.08	36.14
250 keV			
Healthy individuals	3.88	6.39	37.33
Breast cancer patients	3.89	5.17	43.68
500 keV			
Healthy individuals	4.00	7.91	37.86
Breast cancer patients	4.01	5.80	43.14
1 MeV			
Healthy individuals	4.10	9.20	37.31
Breast cancer patients	4.12	6.17	43.69

*Mann–Whitney *U* test compares mean ranks instead of sample mean

Table 3 Z_{eff} descriptive statistics for the two groups of healthy individuals and cancer patients

Group	Mean	SD	Mean rank*
50 keV			
Healthy individuals	18.13	0.62	45.23
Breast cancer patients	17.96	0.44	35.78
100 keV			
Healthy individuals	15.16	0.15	45.13
Breast cancer patients	14.90	0.58	35.88
250 keV			
Healthy individuals	17.83	0.71	45.38
Breast cancer patients	17.64	0.50	35.63
500 keV			
Healthy individuals	19.46	0.63	45.00
Breast cancer patients	19.27	0.57	36.00
1 MeV			
Healthy individuals	19.79	0.60	44.90
Breast cancer patients	19.61	0.57	36.10

*Mann–Whitney *U* test compares mean ranks instead of sample mean

Z_{eff} values for the selected photon energies, obtained for the two groups of individuals.

Box plots of mass attenuation coefficients for 50 keV, 100 keV, 250 keV, 500 keV and 1 MeV are shown in Fig. 2. In the low-energy region, mass attenuation coefficients of the healthy individuals were higher than those for the cancer patients. In contrast, mass attenuation coefficients for the cancer patients were higher at high energies (1 MeV). It is known that the interaction of photons with matter show different behaviors for different energies. Due to the fact that photoelectric effect is dominant in the low-energy region, mass attenuation coefficient change depends on effective atomic numbers. It is noted that in the high-energy region, the Compton effect is dominant. Furthermore, it was observed that the MCNP and ZXCOM results support each other. According to the Kolmogorov–Smirnov test, it was found that the data did not follow a normal distribution. Thus, the Mann–Whitney *U* test was used to explore whether there were any statistically significant differences between the coefficients of the healthy individuals and cancer patients. Electron density values of the cancer patients were found to be higher than those for the healthy individuals at energies of 250 keV, 500 keV and 1 MeV, while they were lower the low-energy region (for 50 keV and 100 keV). The results should be examined separately in the low-energy and high-energy region. It is clearly seen that the differences in electron density observed in the different energy regions and the Monte Carlo simulation results support each other. In addition, differences in the electron density values for the healthy individuals and the cancer patients were found statistically significant at 50 keV and 100 keV (Mann–Whitney *U*

Fig. 2 Box plots of mass attenuation coefficients for 50 keV, 100 keV, 250 keV, 500 keV and 1 MeV

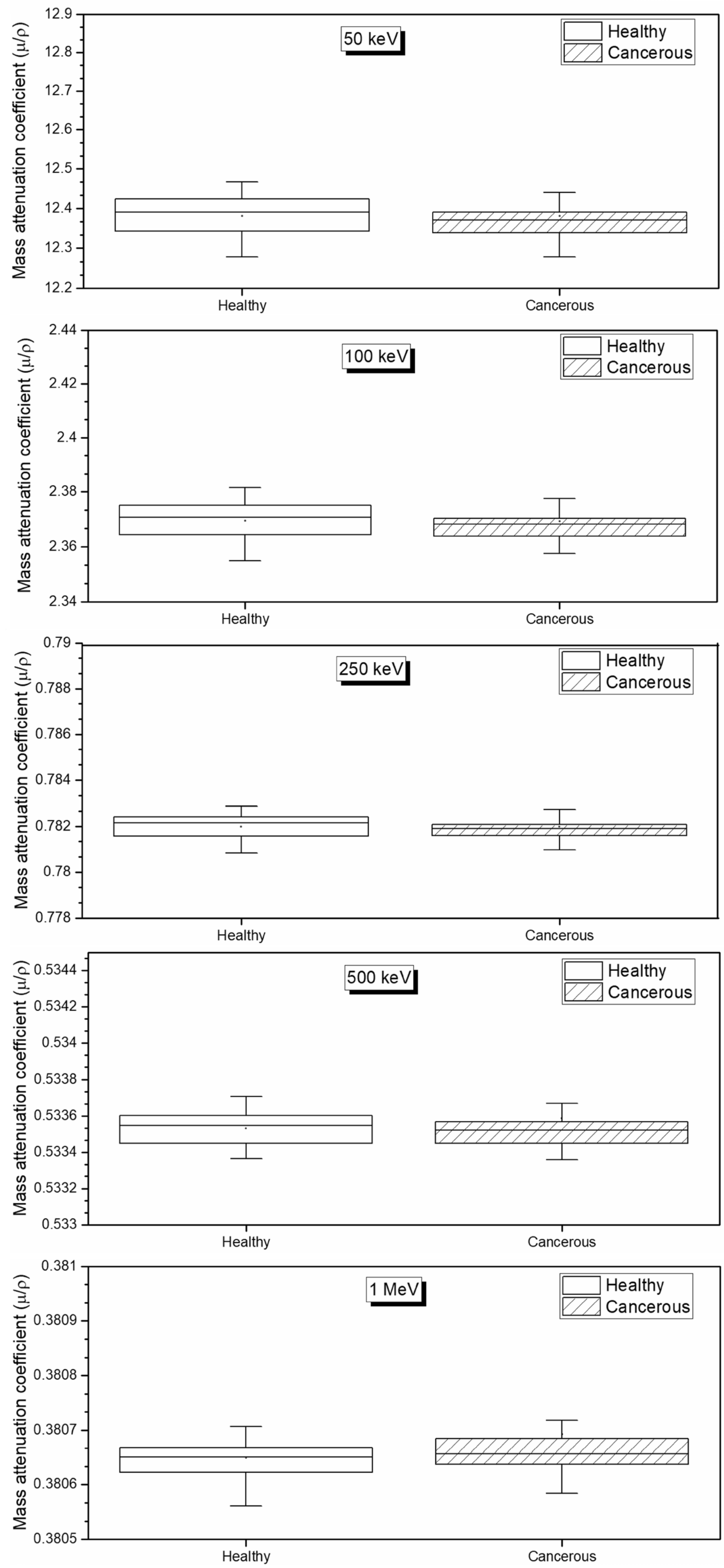

Table 4 Mann–Whitney *U* test of the differences between healthy individuals and cancer patients obtained for N_{el}

	Test statistics				
	50 keV	100 keV	250 keV	500 keV	1 MeV
Mann–Whitney *U*	618.50	625.50	673.00	694.50	672.50
Asymp. sig. (2-tailed)	0.080*	0.089*	0.220	0.309	0.219

*Shows the statistical significance ($p<0.10$)

Table 5 Mann–Whitney *U* test of the differences between healthy individuals and cancer patients obtained for Z_{eff}

	Test statistics				
	50 keV	100 keV	250 keV	500 keV	1 MeV
Mann–Whitney *U*	611.00	615.00	605.00	620.00	624.00
Asymp. sig. (2-tailed)	0.069*	0.075*	0.061*	0.083*	0.090*

*Shows the statistical significance ($p<0.10$)

test, $p<0.10$) (Table 4). In addition, effective atomic numbers were higher for the healthy individuals as compared to the cancer patients, for all selected energies. These differences were statistically significant ($p<0.10$) (Table 5).

Conclusion

In this study, relationships were observed between cancer patients and healthy individuals, in terms of radiation interaction parameters. The μ_m values in blood of the healthy individuals were higher than those of the cancer patients at low-energy regions, while they were lower in blood of the cancer patients at high energy (at 1 MeV). These results were supported by the results obtained with the ZXCOM program. This reinforces and confirms that a relationship may exist between radiation interaction parameters (Z_{eff}, N_{el} and μ_m) and cancer. Thus, radiation interaction parameters may be considered for early diagnosis or treatment of cancer patients. However, further extensive studies for example on other diseases in addition to cancer may be also be useful, the issue of individual variability needs to be studied, and to investigate the performance of the test in terms of true-positive vs true-negative results.

There are numerous studies that have shown alterations in serum/plasma trace elements in patients with breast cancer. However, no studies concerning the evaluation of whole blood μ_m, Z_{eff} and N_{el} values have been performed. In the present study, whole blood samples from breast cancer patients were used to determine μ_m, Z_{eff} and N_{el} and compare the results with those from healthy individuals, to find any differences in μ_m, Z_{eff} and N_{el} values of both groups.

When the Monte Carlo results were considered, higher mass attenuation coefficients were obtained in samples from the healthy individuals as compared to those from the cancer patients, at low energies. This is due to the contribution of the photoelectric effect which is dominant at low photon energies. Since the photoelectric effect is proportional to the atomic number, it can be concluded that the average effective atomic number of blood from the healthy individuals is higher than that in blood from the cancer patients, in this energy region. In contrast, mass attenuation coefficients were higher in blood from the cancer patients as compared to that from the healthy individuals, at 1 MeV. It is a known fact that the Compton effect is dominant at such a high energy. Since the probability of the Compton effect varies with the mean electron density, it can be said that the electron density of blood samples from cancer patients is higher than that of blood from healthy individuals, at 1 MeV. All these MCNP results were supported by the results obtained from ZXCOM.

As mentioned before, radiation interaction parameters may be interpreted separately for different photon energies. As a main result of the present study, photon atomic parameters such as mass attenuation coefficient (μ_m) effective atomic number (Z_{eff}) and electron density (N_{el}) may be considered in the diagnosis or treatment of cancer patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Atatürk University Medical Faculty Ethics Committee, 10.24.2016, session 6, number: 22) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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