Urinary Dielectric Properties for Bladder Cancer

Chao-Zhe Zhu
Jining Medical University
Hua-Nong Ting (tinghn@um.edu.my)
Universiti Malaya
Kwan-Hoong Ng
Universiti Malaya
Kein-Seong Mun
Universiti Malaya
Teng-Aik Ong
Universiti Malaya
Nan Wang
Jining Medical University

Research Article

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Abstract

The study investigated the urinary dielectric properties for bladder cancer in a non-invasive manner. 10 healthy subjects and 10 subjects with bladder cancer were recruited for the study. The urine samples were analyzed using urinalysis and urine cytology assessment. A vector network analyzer was used to measure the dielectric constant (ε') and loss factor (ε'') of urine at microwave frequencies between 0.2 GHz to 50 GHz at 25°C, 30°C, 37°C, respectively. Statistically significant differences in dielectric constant and loss factor were observed between healthy subjects and subjects with bladder cancer especially at frequencies between 25 GHz and 40 GHz at 25°C. Correlation was observed between urinary exfoliated urothelial cell number and the dielectric properties of subjects with bladder cancer at 25°C. Subjects with bladder cancer had statistically significant lower dielectric constant value and higher loss factor value than those of healthy subjects. The dielectric constant correlated negatively with urinary exfoliated urothelial cell number while loss factor correlated positively with urinary exfoliated urothelial cell number.

1. Introduction

Bladder cancer is a common disease of the urinary system. In recent years, the cases have risen steadily, with more than 90% being diagnosed as transitional cell carcinoma, 5% as squamous cell carcinoma and fewer than 2% as an adenocarcinoma [1]. Moreover, men are three to four times more likely to be afflicted with the disease than women [2, 3].

The symptoms mostly present as hematouria, strong urges, frequent and painful micturation. Conventional methods to detect the disease include urine cytology and cystoscopic resection [4–6]. Currently, both methods are also gold standards of diagnosis [7]. But they are invasive and often cause pain and bleeding in patients, with the risk of urinary tract infection and other complications. It is, therefore, of great advantage to patients if an effective non-invasive method of diagnosis is developed.

The dielectric properties of biological fluids and tissues, such as the dielectric constant (ε') and loss factor (ε''), have been studied for tissues of human and animals [8–16]. Besides that, the dielectric properties have also been characterized between normal tissues and tumorous tissues [13–15]. Tumorous breast tissues were reported to have higher value of dielectric properties than that of normal breast tissues between 0.5 GHz and 50 GHz [13]. Tumorous liver tissues had higher values of complex permittivity than that of normal liver tissues at 2.45 GHz and 5.8 GHz [14]. For skin cancer, malignant squamous cell carcinoma (SCC) was found to have statistically significant higher dielectric constant but lower loss factor than those of the normal SSC at 11 frequency points between 0.5 GHz and 50 GHz [15]. Malignant basal cell carcinoma (BCC) was reported to have statistically significant higher dielectric constant and loss factor than those of normal BCC at 11 frequency points between 0.5 GHz and 50 GHz [15]. The dielectric properties of bladder tissues were studied in porcine and bovine between 0.5 GHz and 20 GHz [12]. Before the cross-over point, the relative permittivity of bovine was higher that of porcine and after the cross-over point, the relative permittivity of bovine was less than that of porcine. These studies, however, are invasive and require tissues to be removed from the body. Dielectric properties were studied for the DNA of urine of health subjects and subjects with bladder cancer together with the Telomerase activity and Cytokeratin 20 [17]. The dielectric properties of subjects with bladder cancer were reported to be higher than those of healthy subjects.

Exfoliated epithelial cells in urine may be used as an important marker in diagnostic of bladder disease. Changes in cell metabolism have been found to correlate well with electrochemical exchanges in the cell membrane. Thus, critical alterations in the cell's biological functions may be gleaned by analyzing these electrical signals [10, 18, 19]. One of the most important events in the formation of cancer is the disruption and deterioration of electrochemical patterns on the cell membrane, which is a key indicator of the primary stages of carcinogenesis [20–22]. In addition, metastatic progression of cancer cells will also lead to bioelectrical disruption at the effected tissues [23, 24].

Limited study is reported for measuring the urinary dielectric properties for bladder cancer. This study investigates the non-invasive method of characterizing the dielectric properties of urine of bladder cancer. The study investigates the dielectric properties of urine of subjects with bladder cancer and healthy subjects at microwave frequencies between 0.2GHz and 50GHz and at three different temperatures. The correlation between the tumorous cell number and dielectric properties is studied.

2. Materials And Methods

2.1 Sample Preparation

The urine samples were obtained from 10 healthy subjects and 10 subjects with bladder cancer aged between 40 years and 80 years. The samples were sent for routine biomedical and pathological microscopy analyses. The participants were comprised of patients admitted to Universiti Malaya Medical Centre (UMMC), Kuala Lumpur, Malaysia. Written and informed consent were obtained from the participants before urine collection. Medical ethics approval was obtained from the Institutional Ethics Review Committee of UMMC (No. 2016816-4143). All methods were performed in accordance with the relevant guidelines and regulations.

2.2 Sample Collection

A minimum of 60 ml of mid-stream urine was collected in sterile container for each subject. The container was labeled with the subject's name and date of collection. Then, it was immediately placed in a sealed bag and stored at 4°C. No preservatives were added and to ensure that the urine was processed as fresh as possible, all samples were sent for analyses within four hours of collection.

2.3 Urine Analysis

About 20ml of each urine sample was sent to the Division of Laboratory Medicine in UMMC for analysis of protein, glucose, ketone, haemoglobin, bacteria, urea, sodium and potassium using a Roche Cobas® U601 urine analyser (F. Hoffmann-La Roche Ltd, Basel, Switzerland).

Meanwhile, 10ml of each urine sample was sent to the Pathology Department of the Faculty of Medicine, University Malaya, for microscopic examination using the ThinPrep® 2000 system (Hologic Canada ULC, Ontario, Canada). Urine samples that were positive for hematuria and diabetes were excluded.

2.4 Measurement of Dielectric Properties

Measurement of urine dielectric properties was performed at the Electromagnetic Laboratory at the Faculty of Engineering, Universiti Malaya. The equipment consists of an Agilent E8364C personal network analyzer and Agilent 82357A GPIB interface controlled by the Agilent 85070 software (Agilent Technologies, Santa Clara, California, USA) and a 50GHz open-ended coaxial probe with flexible cable (2.2mm diameter, 20cm long). The experimental setup is shown in Fig. 1.

2.5 Experimental Analysis Process

The vector network analyzer was calibrated with distilled water and air as references. As the standard for refresh calibration, the electronic-calibration (E-Cal) was used. Random systemic errors were taken into account to decrease uncertainties [25]. The Agilent vector network analyzer is a reliable device, especially for measuring small quantities of liquids, as it provides more frequency points than resonant cavity methods, although the latter is a more accurate factor. It can also take measurements in a wider microwave frequency range [26, 27].

The front of the open-ended coaxial probe was placed in the urine samples, with the other end connected to the vector network analyzer. The probe was cleaned with distilled water and sterilized with alcohol wipes after measuring each sample. The probe was immersed into the sample at a depth of more than 2 cm while ensuring that there were no air bubbles trapped at its end. The relative position of the probe was maintained throughout each measurement to achieve good and consistent reading. Each urine sample was measured three times. The measurements were conducted at 25°C, 30°C and 37°C using a water bath (Memmert WNB7, Duesseldorf, Germany), respectively. The range of the temperature fluctuation was ± 0.1°C. In this study, dielectric constant, ε' and loss factor, ε'' of the urine samples were measured at microwave frequencies between 0.2GHz and 50GHz, with a total of 250 frequency points.

2.6 General Complex Permittivity Theory

The molecules in liquids would become polarized under the influence of an electrical field. The major composition of urine is water, accounting for 95% of its specific gravity. Thus, a highly polarized molecules could be expected to be the primary contributor to permittivity [28].

The earliest studies on polar dielectrics and modeling could be traced back more than 70 years by Debye [29]. The dielectric relaxation response could be well-represented by the Debye model [30–32]. This study was based on the Debye model. The single-Debye equation was applied to solve the problem of curve-fitting and the MATLAB function was used to complete the drawing of the figure according to Eq. 1.

$$\epsilon^* = \epsilon_\infty + \frac{\Delta\epsilon}{1 + j\omega\tau} - j\frac{\sigma_s}{\omega\epsilon_v}$$

1

where

ϵ^* = complex permittivity

ϵ_∞ = infinite frequency permittivity

$\Delta\epsilon$ = magnitude of dispersion

ϵ_v = vacuum permittivity (ϵ_v=8.854 PF/m)

ω = angular frequency (ω = 2πf) (rad/s)

τ = dielectric relaxation time

σ_s = static conductivity (S/m)

To ensure that the formula was feasible, the parameters ϵ_∞, $\Delta\epsilon$, τ and σ_s were set at a reasonable range ($\epsilon_\infty \geq 1$, $\Delta\epsilon \geq 0$, $\tau \geq 0$ and $\sigma_s \geq 0$). A study had been conducted to compare the dielectric properties of bodily fluids with the Debye model in the frequency range of between 200MHz and 10GHz and at 37°C [33]. The polarization of porcine urine was observed to fit the Debye model at a frequency range of 50MHz to 20GHz [34]. The dielectric properties data of urine of healthy subjects were used Eq. (1) for fitting with Debye data at 25°C and in the frequency range of 0.2 to 50GHz, and the experimental results were closely matched with Debye model [35].

2.7 Data Analysis

Dielectric properties were measured in terms of dielectric constant (ϵ’) and loss factor (ϵ”), between 0.2GHz and 50GHz with a total of 250 frequency points. SPSS statistic 21.0 software was used to perform the statistical analyses. Independent Samples T-test was used to determine the statistically significant difference in dielectric properties between normal subjects and bladder cancer subjects. One-way ANOVA was used to determine the temperature effect on the dielectric properties. The Pearson correlation analysis was used to determine the correlation between urinary exfoliated urothelial cells with the dielectric properties. The significance level was set at $p < 0.05$ for all the statistical analyses.

3. Results

3.1 Effect of urine composition

The results of urine analysis and microscopy test are shown in Table 1 and Table 2 respectively. No statistically significant difference was reported between healthy subjects and subjects with bladder cancer for urea ($t = 1.806$, $p > 0.05$), sodium ($t = 0.15$, $p > 0.05$), potassium ($t = 0.916$, $p > 0.05$), pH ($t=-0.643$, $p > 0.05$), squamous cells ($t = 1.04$, $p > 0.05$) and inflammatory cells ($t=-2.316$, $p > 0.05$). However, statistically significant difference was observed between healthy subjects and subjects with bladder cancer in urinary exfoliated urothelial cell number ($t=-23.447$, $p < 0.001$). Urine ThinPrep® smears test result for one healthy subject and one subject with bladder cancer is shown in Fig. 2.

Table 1
Urine analysis test results

Group Component	**1** **Healthy** **(Mean ± SD)**	**2** **Bladder Cancer** **(Mean ± SD)**
Sample size (n)	10	10
Age (years)	65 ± 5	55 ± 6
pH	6 ± 0.7	6.5 ± 0.5
Protein (mg/dl)	0	0
Haemoglobin (mg/dl)	0	0
Glucose (mg/dl)	0	0
Ketone (mg/dl)	0	0
Bacteria	Nil	Nil
Urea (mmol/L)	192 ± 124	117 ± 49
Sodium (mmol/L)	85 ± 32	91 ± 31
Potassium (mmol/L)	30 ± 15	22 ± 8

Table 2
Microscopy test results

Group Component	1 Healthy (Mean)	2 Bladder Cancer (Mean)
Sample size (n)	10	10
Squamous cells (cells/mL)	5	6
Inflammatory cells (cells/mL)	3	7
Urothelial cells (cells/mL)	0	78
Total cells (cells/mL)	8	91

3.2 Effect of frequencies on dielectric properties

The mean relative dielectric constant (ε’) and loss factor (ε”) of urine of subjects with bladder cancer at three different temperatures are shown in Fig. 3. Dielectric constant increased its value starting 0.2 GHz and decreased after reaching its peak value. Similar pattern was observed for loss factor. At frequencies lower than 1 GHz, the dielectric constant was high while the loss factor was low. This can be explained that more than 95% of the urine is water and the water has high dielectric property and particular relaxation characteristic[36]. At middle frequencies about 20 GHz, the dielectric constant changed to low value while the loss factor changed to high value. This is due to the dielectric relaxation process of pure water undergoing capacitance charging and discharging [37, 38]. At high frequencies of more than 20 GHz, the dielectric constant and loss factor represented a relatively stable process of reduction. This is due to that the pure water has the characteristics of low insulation and high conductivity at high frequency field [37, 39].

3.3 Comparison between healthy subjects and subjects with bladder cancer across three temperatures

The mean dielectric constant and loss factor of urine of health subjects and subjects with bladder cancer at three different temperatures are shown in Fig. 4. Crossing points of 7.4 GHz and 26.8 GHz were observed respectively for dielectric constant and loss factor. Before the crossing points, the dielectric constant and loss factor were observed to have higher value at 25°C compared to those at other temperatures while after the crossing points, they were at lower values compared to those at other temperatures. The dielectric constant and loss factor decreased with the temperature before the crossing point while they increased with the temperature after the crossing point. It was observed that the dielectric constant of the urine of subjects with bladder cancer was slightly lower than that of healthy subjects while the loss factor of the urine of subjects of bladder cancer was slightly higher than that of healthy subjects.

Figure 5 and Figure 6 showthe dielectric constant and loss factor respectively for health subjects and subjects with bladder cancer at frequencies between 25 GHz and 40 GHz at 25°C.

3.4 Correlation between urinary exfoliated urothelial cell number and dielectric properties

Correlation analysis was conducted to determine the correlation between urinary exfoliated urothelial cell number and dielectric constant and loss factor of urine of subjects with bladder cancer. The maximum Pearson correlation coefficient, r is shown in Table 3 for dielectric constant and loss factor at three temperatures. The maximum Pearson correlation coefficients were reported at 25°C for dielectric constant ($r = -0.662$, $p < 0.05$) and loss factor ($r = 0.664$, $p < 0.05$). Dielectric constant correlated negatively with the urinary exfoliated urothelial cell number while loss factor correlated positively with the urinary exfoliated urothelial cell number.

Table 3
Maximum correlation between urinary exfoliated urothelial cell number and dielectric constant and loss factor at three different temperatures

Temperature (°C)	ε'			ε''		
	Frequency point (GHz)	Maximum r-value	p-value	Frequency point (GHz)	Maximum r-value	p-value
25	5.0	-0.662	0.03	40.6	0.664	0.02
30	25.4	-0.630	0.04	49.0	0.598	0.05
37	3.4	-0.597	0.07	41.6	0.4359	0.08

4. Discussion

Statistically significant differences in dielectric constant were observed across the three temperatures with the highest F number at 35.8 GHz ($F = 1576.3$, $p < 0.05$). Statistically significant differences in loss factor were observed across the temperatures as well with the highest F number at 21 GHz ($F = 1759.1$, $p < 0.05$). The impact of temperature on dielectric properties may be due to the molecular movement and hydrogen bonds in urine when the temperature changes [40]. The relaxation time is shortened. When the temperature increased, the viscosity of the solution decreased due to the increment in movement and ion mobility within it. Thus, with the effect on the viscosity of the solution, relaxation frequency was inversely proportional [40, 41].

The dielectric properties of cells are related to the properties of cell walls, the cell membrane is close to the inside of the cell wall, i.e. the area where the charge is generated. There is “leaky” dielectric fields in these cells, thus any changes can influence the dielectric properties of cells. The kinematic viscosity of human urine is essential to accurate modeling of heat transfer and fluid mechanics during hyperthermia treatment of bladder cancer, and it is temperature-dependent and always higher (approximately 10%) than pure water (within 20–42°C). Due to the lack of tissue properties reports, the detection of bladder disease has been dealt with an estimated 'effective thermal conductivity' parameter that try to imitate the integrative effect of conduction and convection within the bladder wall and bladder urine[42]. A few studies also have used urothelial cells to detect premalignant urothelial lesions and urothelial carcinoma [17, 43].

No statistically significant differences were reported in dielectric properties between healthy subjects and subjects with bladder cancer for frequencies between 0.2 GHz and 25 GHz, and between 40 GHz and 50 GHz. Statistically significant differences in dielectric constant and loss factor were reported between the two groups in the frequencies between 25 GHz and 40 GHz. For frequencies between 25 GHz and 40 GHz, subjects with bladder cancer had statistically significant lower dielectric constant value and higher loss factor value than those of health subjects. However, t values of less than ± 3.0 were observed for the T test statistical analysis. The reason for this difference can be explained by the presence of urinary exfoliated urothelial cells that were increased in subjects' urine, and cancerous cells have lower electrical impedance and electrical membrane potential.

Urinary exfoliated urothelial cells are closely related to bladder cancerous disease [44, 45]. Fluorescence in situ hybridization (FISH) of urinary exfoliated urothelial cells has been successfully in detecting bladder cancer in voided urine and the urine markers can be used to predict its recurrence [44]. In addition, some current methods (such as UroVysion analysis, telomerase test, BTA stat test and hemoglobin dipstick test) are already being used to detect urothelial carcinoma in urine, and by comparing these methods, each method has different properties for sensitivity and specificity [45].

5. Conclusion

Urinary dielectric properties of healthy subjects and subjects with bladder cancer were determined at Microwave frequencies between 0.2 GHz and 50 GHz at 25°C, 30°C and 37°C, respectively. No statistically significant differences were reported between healthy subjects and subjects with bladder cancer for urea, sodium, potassium, pH, squamous cell number and inflammatory cell number. The dielectric constant and loss factor decreased with the temperature before the crossing point while they increased with the temperature after the crossing point. Statistically significant differences were reported in dielectric constant and loss factor between the temperatures. Statistically significant differences in dielectric constant and loss factor were observed between healthy subjects and subjects with bladder cancer especially at frequencies between 25 GHz and 40 GHz at 25°C. Subjects with bladder cancer had statistically significant lower urinary dielectric constant value and higher urinary loss factor value than those of health subjects. Correlation was observed between urinary exfoliated urothelial cell number and the dielectric properties of subjects with bladder cancer. The dielectric constant correlated negatively with urinary exfoliated urothelial cell number while loss factor correlated positively with urinary exfoliated urothelial cell number.

Declarations

Data Availability

The datasets used and/or analysed during the current study are available fromthe corresponding author onreasonable request.

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Authors' contributions

Chao-Zhe Zhu performed experiments, analyzed data and wrote the manuscript. Hua-Nong Tin, Kwan-Hoong Ng and Kein-Seong Munconceptualized the idea and revised the manuscript. Teng-Aik Ong, Kein-Seong Mun and Guan-nan Wang provided experimental support. All authors approved the final manuscript.

Consent for publication

All authors read and agreed for publication.

Competing interests

All authors declare that they have no competing interests.

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Figures

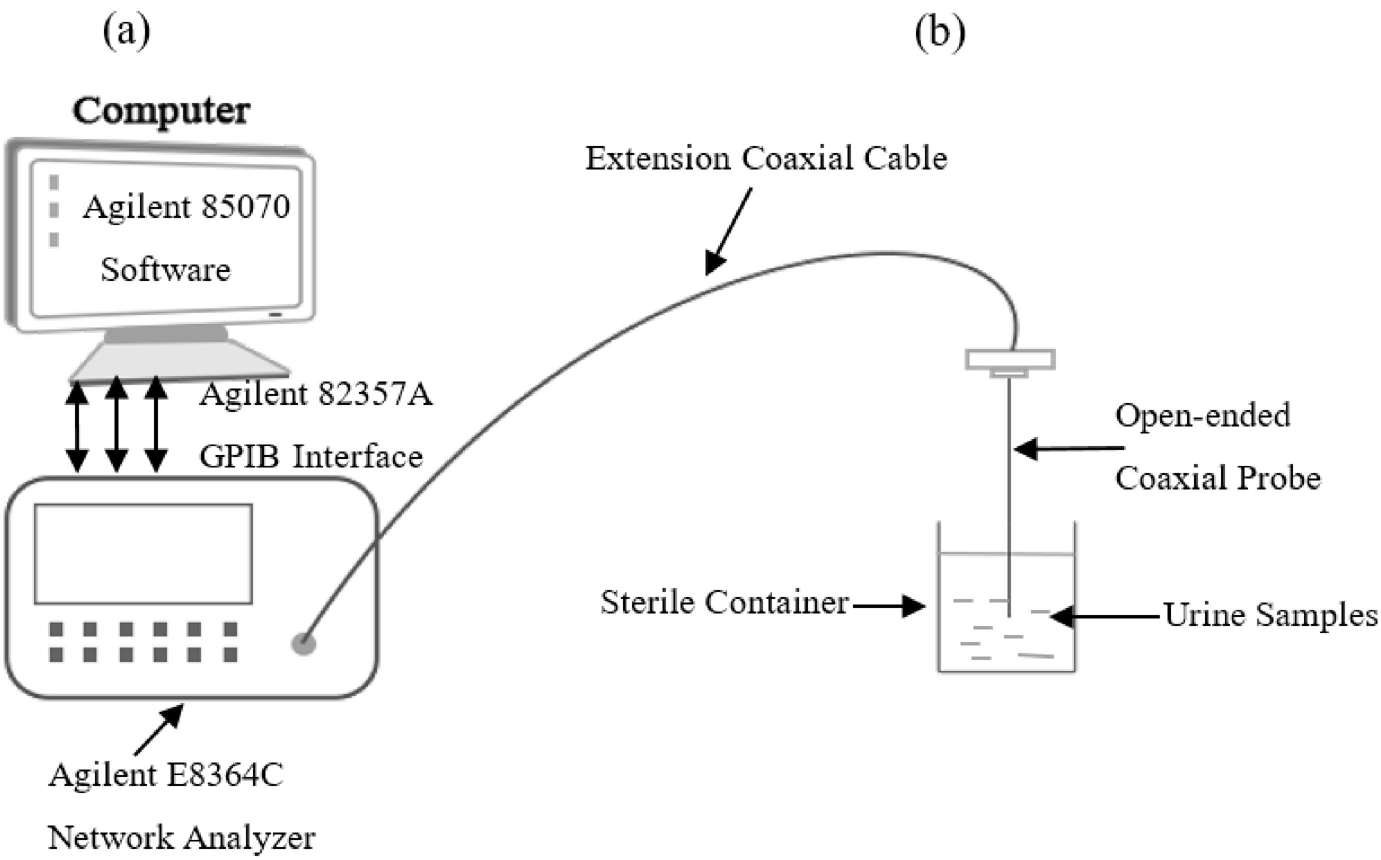

Figure 1

Experimental setup to measure urine dielectric properties

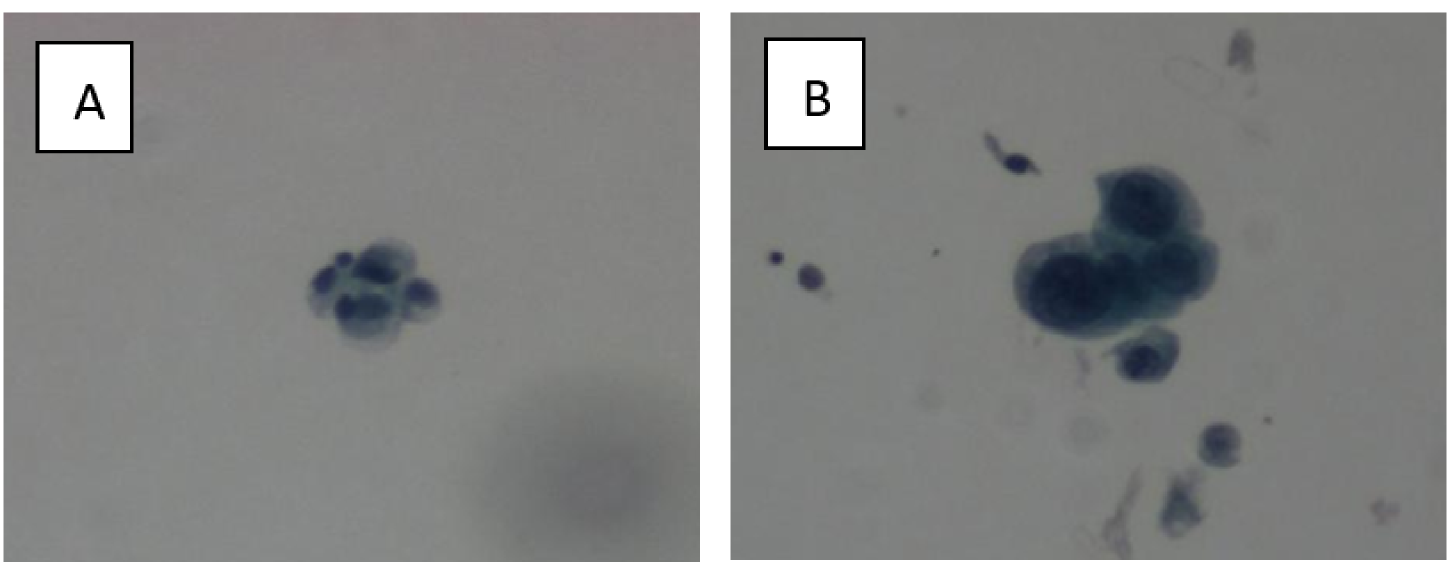

Figure 2

Urine ThinPrep® smears (A) Health subject: A small cluster of benign transitional cells exhibiting small uniform nucleus and abundant cytoplasm. The urine in the background is clean [Papanicolaou (Pap) stain, x100 original magnification]; (B) Subject with bladder cancer: urine exhibits a cluster of highly dysplastic cells. These cells have pleomorphic hyperchromatic nucleus and reduced cytoplasm (high nucleo-cytoplasmic ratio, i.e. a feature of malignancy). The background shows scattered inflammatory cells [Pap stain, x100 original magnification].

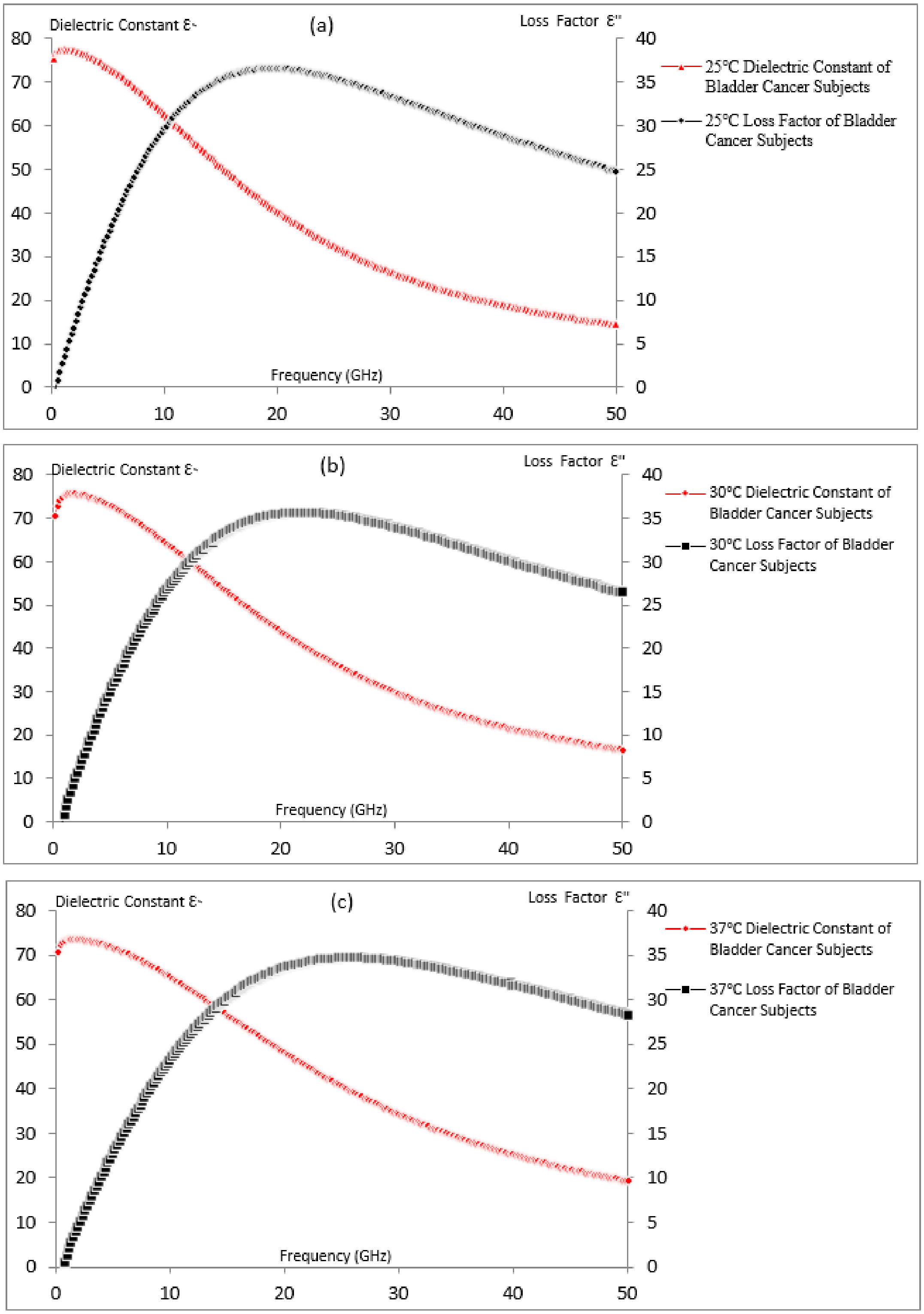

Figure 3

Mean dielectric constant (ε') and loss factor(ε") of subjects with bladder cancer at (a) 25°C, (b) 30°C and (c) 37°C

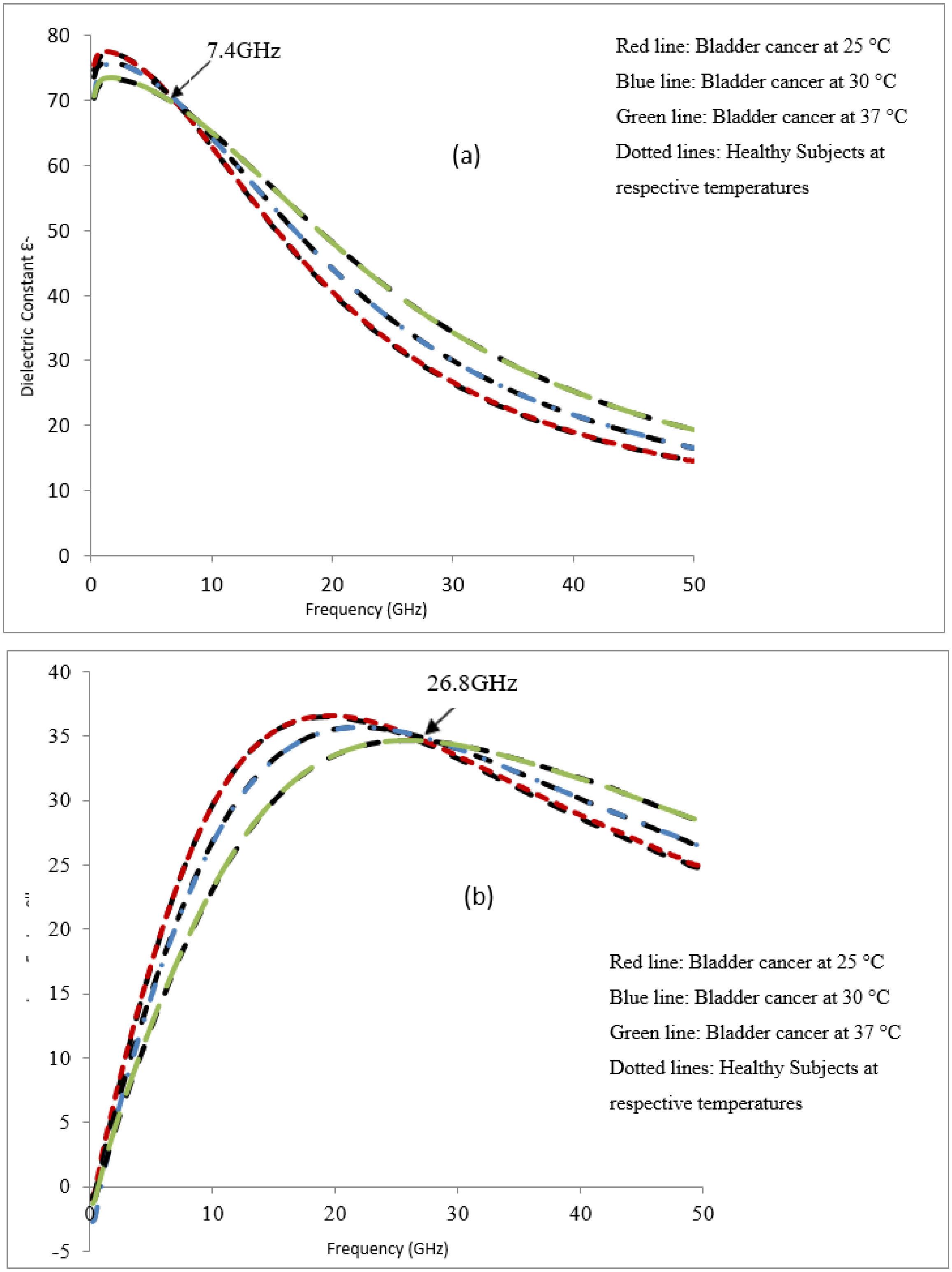

Figure 4

(a) Mean dielectric constant (ε’) and (b) Mean loss factor (ε”) of urine of healthy subjects and subjects with bladder cancer at 25°C,30°C and 37°C.

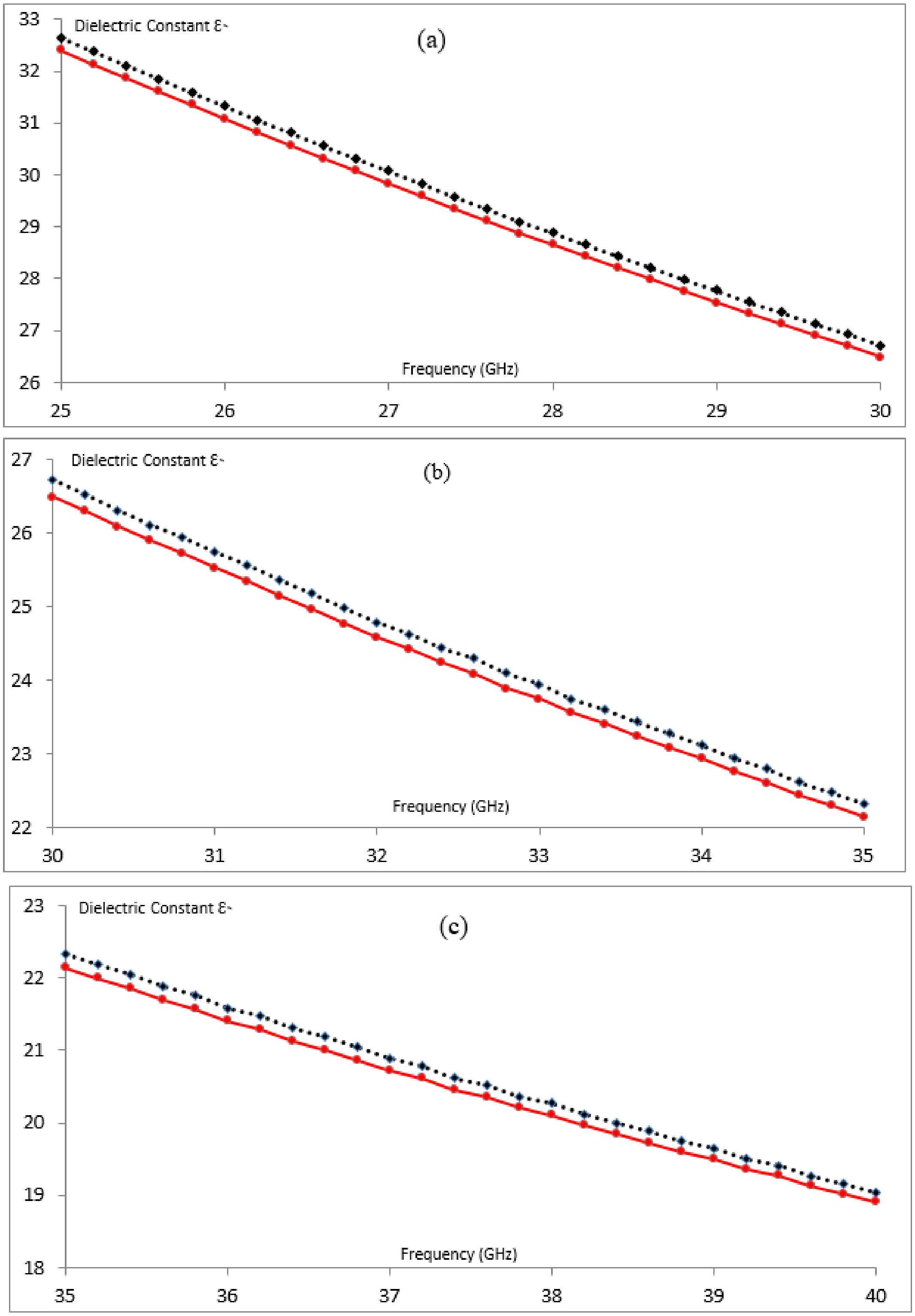

Figure 5

Dielectric constant of urine of healthy subjects and subjects with bladder cancer measured at 25°C. (a) Frequencies between 25 GHz and 30 GHz, (b) Frequencies between 30 GHz and 35 GHz, (c) Frequencies between 35 GHz and 40 GHz. Black dotted line represents dielectric constant of urine of healthy subjects, while red solid line represents dielectric constant of urine of subjects with bladder cancer.

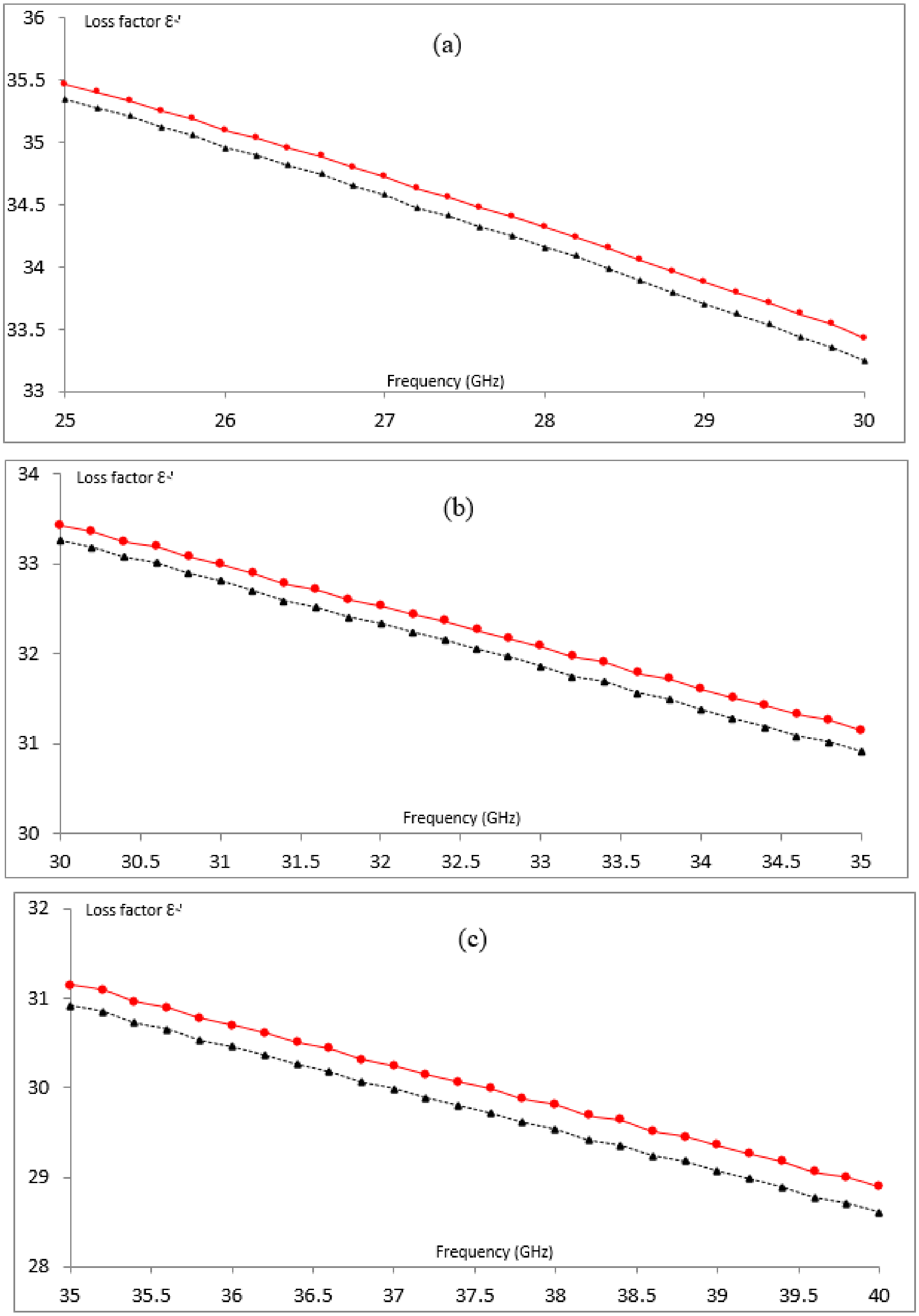

Figure 6

Loss factor of urine of healthy subjects and subjects with bladder cancer measured at 25°C. (a) Frequencies between 25 GHz and 30 GHz, (b) Frequencies between 30 GHz and 35 GHz, (c) Frequencies between 35 GHz and 40 GHz. Black dotted line represents loss factor of urine of healthy subjects, while red solid line represents loss factor of urine of subjects with bladder cancer.