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Research paper

Forest adjuvant anti-cancer therapy to enhance natural cytotoxicity in urban women with breast cancer: A preliminary prospective interventional study

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ABSTRACT

Introduction: Studies have shown both significantly diminished natural cytotoxicity and immunosuppression in breast cancer patients after standard anti-cancer treatments. Therefore, an integrative approach employing adjuvant therapy in addition to current treatments is required to enhance immunoactivation. This preliminary prospective interventional study aimed to assess the feasibility of forest therapy as an adjuvant to enhance natural cytotoxicity.

Methods: This was a feasibility study of 11 volunteer women aged 25–60 years with stage III breast cancer. All subjects were exposed to daily forest therapy for 14 days whilst living in accommodation in a forest. Interventions included a relaxing daily 2-h morning walk (3 miles), free time tailored to subjects interest, group interaction and prepared meals based on nutritional standards. Outcome measures included natural killer (NK) cell populations and levels of perforin and granzyme B.

Results: Data from all participants were analysed. The mean volume of NK cells increased from 319.4 μL in the city to 444.6 μL in the forest after forest therapy ($p < 0.01$). The mean level of perforin increased from 216.9 pg/mL in the city to 344.9 pg/mL in the forest and then further increased to 463.2 pg/mL after subjects returned to the city ($p < 0.02$). The mean level of granzyme B increased from 4.4 pg/mL in the city to 11.2 pg/mL in the forest and then further increased to 20.2 pg/mL after subjects returned to the city ($p < 0.02$).

Conclusions: This study demonstrates the potential of forest therapy as an adjuvant anti-cancer therapy after standard treatments. A definitive trial with a control group should now be performed with larger sample sizes and long-term follow-up periods to confirm the feasibility and potential therapeutic effectiveness of this approach.

1. Introduction

Breast cancer, the most frequently diagnosed cancer in women worldwide, has been reported to account for 23% of all new cases of cancer in women since the beginning of the millennium [1]. The incidence rate of breast cancer has been increasing due to recent increases in screening activity and intensity, especially in economically developing countries [2]. Conversely, breast cancer mortality rates have been decreasing due to the early application of standard anti-cancer treatments such as surgery, radiotherapy, or chemotherapy with early detection strategies including mammography [1,3].

Despite the advanced treatment strategies for breast cancer, various studies [4–9] have shown that immunosuppression is common after standard anti-cancer treatments, and that natural killer (NK) cell activity is particularly suppressed. NK cells are cytolytic effector lymphocytes of the innate immune system that are especially critical for immune surveillance of tumours [10–12]. As it has been observed that peripheral blood natural cytotoxicity is diminished significantly in breast cancer patients, stimulation of NK cell activity after standard anti-cancer treatments has been considered important for breast cancer patients [10,11]. In addition, the activation of the NK cells that produce anti-cancer proteins such as perforin and granzymes when targeting cancer cells has been found to play a critical role in the host anti-cancer defence mechanisms [12]. Therefore, to minimise

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immunosuppression and enhance NK cell activity, an adjuvant anti-cancer therapy after standard treatments is needed.

Recent studies [13–15] conducted in Asian countries have reported that spending time in a forest environment and engaging in activities in the forest such as forest walking or forest bathing trips enhances NK cell activity to induce increased levels of anti-cancer proteins in healthy subjects.

The beneficial effect of this natural environment on NK activity is considered to be related to the enhanced psychoneuroimmunological effects brought about by the reduction in psychological stress experienced in the forest [16–19]. In addition, increased exposure to volatile chemical substances derived from trees such as phytoncides in the forest is considered to lead to stimulation of the proliferation of NK cells [13,18,20]. However, there have been no trials conducted to investigate the use of forest therapy as an adjuvant therapy to improve natural immunoactivation for breast cancer patients.

In this study, we aimed to evaluate the feasibility of forest therapy as an adjuvant anti-cancer therapy by measuring the NK cell population, and levels of two NK cell-released intracellular cytolytic molecules, in breast cancer patients who had undergone standard anti-cancer therapies.

2. Methods

2.1. Participants

Women with breast cancer living in a metropolitan area who were not exposure to a forest environment since being diagnosed with breast cancer were invited to participate in the study through the Korean Breast Cancer Society. No formal sample size calculation was performed because this was a preliminary feasibility study. Eligibility criteria included stage I to III breast cancer; city residence; completion of standard treatments including surgery, radiotherapy, and/or chemotherapy. Twelve female volunteers who met the eligibility criteria were interviewed and screened by research medical doctors at Korea University Hospital. Exclusion criteria included; current smoker, pregnant, current alcohol user, diabetes mellitus, presence of metastasises, infection, serious physical disability, or a mental disorder. One woman withdrew from the study at the beginning of the stay in the forest (day 1) owing to a family matter. The remaining 11 women (aged 25–60 years) completed the forest therapy and all measurements. The study protocol was approved by the Institutional Review Board of Korea University Hospital (AN11043-002), and all participants ($n = 11$) provided written informed consent.

2.2. Forest therapy

All participants travelled by shuttle bus in the summer season to the designated forest, named Saneum Natural Recreational Forest, located in the National Park in Gyeonggi Province in South Korea and close to the metropolitan area (a distance of 40 miles from Seoul). All subjects stayed at log cabins in the forest for 14 days and underwent daily forest therapy. In forest therapy, all subjects spent 2 h every morning (9:30 am–11:30 am) walking outside (3 miles). The participants additionally had the option to spend their free time in the afternoon inside or outside in the forest engaged in reading, writing, sewing, chess, photography, or drawing, depending on the participants' interests. All subjects socially interacted with each other in the forest during the study. All participants were provided daily meals and snacks designed based on general nutritional standards by a nutritionist from the Nutrition Department at Korea University Anam Hospital. Research medical doctors supervised the medical conditions of participants in the forest and provided any medical support when required. No physical or psychological side effects or complications from the forest therapy were reported by any subject during individual interviews with the researchers and allocated medical doctors.

2.3. Measurement parameters

The outcome measures to assess the results of the forest therapy were the NK cell population and the levels of perforin and granzyme. Blood samples were collected by research nurses at the hospital and in the forest in the morning using collection tubes containing an anticoagulant. The samples were sent to the laboratory of the Department of Bio-pathological Diagnosis at Korea University Hospital within 4 h after blood collection. Three sets of blood samples were collected. The baseline blood sampling was conducted at the hospital on the day of the subjects' departure to the forest (day 1). The second blood samples were collected in the forest on the last day of the subjects' 2-week stay in the forest (day 14). The final, follow-up blood sampling was conducted at the hospital a week after the subjects' returned home from the forest (day 21). To measure the NK cell population, flow cytometric analysis was performed using the Cytomics FC 500 flow cytometer (Beckman Coulter, Inc., Brea, CA, USA) according to the manufacturer's protocol. 100 μL of the blood sample was mixed with 10 μL of $CD45^+$-ECD monoclonal antibody and 20 μL of CD3-FITC/CD56-PC5 monoclonal antibody. All the fluorochrome-conjugated antibody reagents and cell fixing and lysing solutions (VersaLyse Lysing Solution) were purchased from Beckman Coulter.

Levels of perforin and granzyme B were measured in serum and plasma samples using commercially available enzyme-linked immunosorbent assay (ELISA) kits (Abcam Biotechnology Co., Ltd., Cambridge, UK) according to the manufacturer's protocol.

2.4. Statistical Analysis

Outcome variables were summarised as means ± standard deviation (SD). All data were confirmed to be normally distributed using the Shapiro–Wilk test. The comparisons of within-group differences of the outcome measures were analysed using paired *t*-tests. SPSS statistical software (Version 12.0, SPSS Inc., Chicago, IL, USA) was used for the analyses. Two-sided tests and a significance level of 0.05 were used for all statistical analyses.

3. Results

All subjects ($n = 11$) who completed the study including the designated forest therapy had similar measurements with respect

Table 1
Characteristics of the subjects at baseline (Day 1).

Characteristics*	Subjects ($N = 11$)
Age, yr	56 ± 5.12
Marital status, no. (%)	
Married	11 (100)
Single or divorced	0 (0)
Type of surgery, no. (%)	
Modified radical mastectomy	11 (100)
Parietal mastecotmy	0 (0)
Postoperative Treatment, no. (%)	
Chemotherapy	11 (100)
Radiotherapy	11 (100)
Stage of breast cancer	
Stage II	0 (0)
Stage III	11 (100)
Stage IV	0 (0)

to the marital status, type of treatments received, and stage of breast cancer (Table 1).

3.1. NK Cells

All parameters used to assess natural cytotoxicity were improved by forest therapy intervention (Fig. 1). The mean number of NK cells had increased by 39% (319.4 μL on day 1 in the city *vs.* 444.6 μL on day 14 in the forest, $p < 0.01$) after forest therapy (Table 2). This elevated population of NK cells subsequently decreased after return to the city (361.8 μL on day 21). This was still 13% higher than the baseline count performed on day 1, although this was not a significant difference (319.4 μL on day 1 in the city *vs.* 361.8 μL on day 21 upon return to the city, $p = 0.06$) (Table 2).

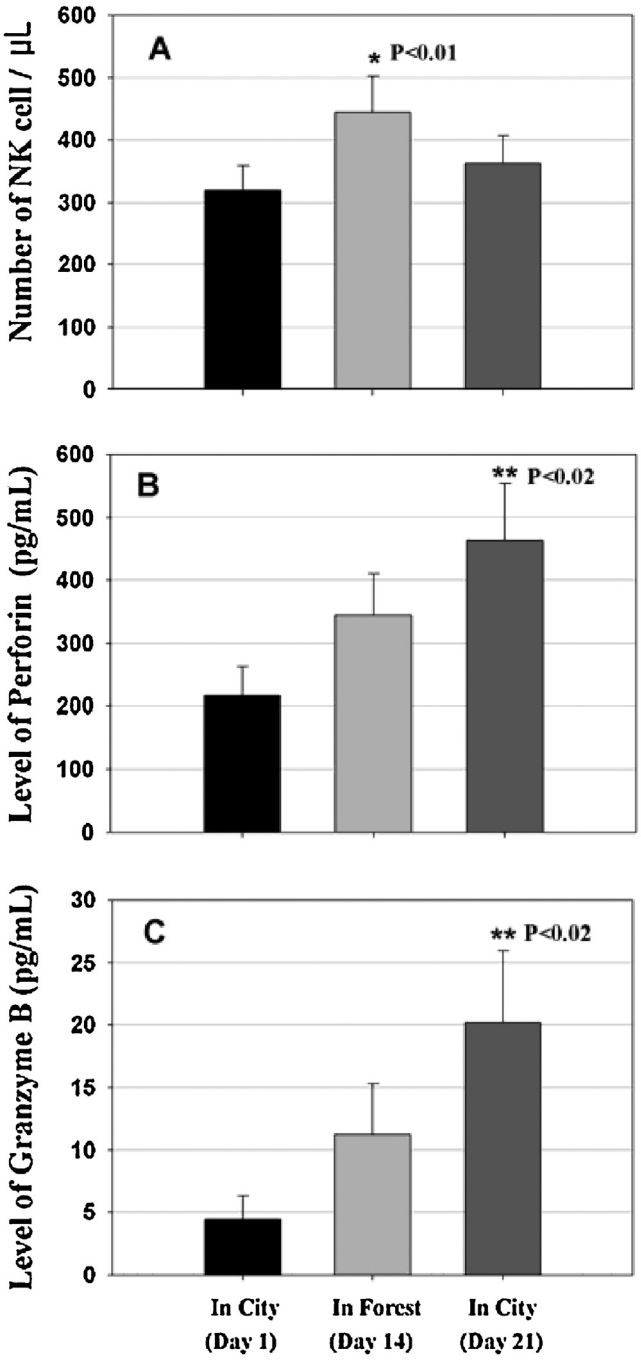

Fig. 1. Effect of forest therapy on NK population (A) and level of perforin (B) and granzyme B (C). Data are presented as the mean + SEM ($n = 11$). *: $p < 0.01$, **: $p < 0.02$, significantly different from before the forest therapy (Day 1) by the paired *t*-test.

3.2. Perforin and Granzyme B

Perforin and granzyme, both intracellular cytolytic molecules, displayed a similar pattern of improvement with forest intervention (Fig. 1). The mean level of perforin increased by 59% after 2 weeks in the forest (216.9 pg/mL on day 1 *vs.* 344.9 pg/mL on day 14) (Table 2). This had increased even more significantly, by 113%, after a subsequent week upon subjects' return to the city (216.9 pg/mL on day 1 *vs.* 463.2 pg/mL on day 21, $p < 0.02$) (Table 2). There was also a 152% increase in the levels of granzyme B between baseline and post-intervention (4.4 pg/mL on day 1 *vs.* 11.2 pg/mL on day 14) (Table 2). In a pattern similar to that of perforin, levels of granzyme B had increased by a total of 459% during the 21-day study (4.4 pg/mL on day 1 *vs.* 20.2 pg/mL on day 21, $p < 0.02$) (Table 2).

4. Discussion

In this study, we showed the clinical ability of forest therapy to enhance natural cytotoxicity in city women diagnosed with breast cancer who had previously undergone standard anti-cancer therapies. This was evidenced by both an increased number of NK cells, and increased levels of perforin and granzyme B, both anti-cancer molecules. Furthermore, this study indicates the feasibility of forest therapy as an adjuvant therapy for breast cancer. This new type of adjuvant therapy uses the natural environment and showed no adverse side effects during this study.

The beneficial effects of forest activities on other clinical conditions such as hypertension [21,22], diminished pulmonary function [23] or diabetes [24], have been reported. Recent studies have also shown that forest activities reduce stress hormone levels [19] and regulate autonomic function [25]. With regard to human immunity, in studies by Li et al. [13,15,26] forest activities were found to increase NK cell activity and the expression of anti-cancer proteins in healthy subjects. Moreover, this increase in natural cytotoxicity improved more than in subjects dwelling in the city during the same time. Despite growing evidence for the ability of forest therapy to enhance natural cytotoxicity, no large-scale trials have yet been conducted. The present study, to our knowledge, is the first to evaluate the feasibility of forest therapy as adjuvant anti-cancer therapy for breast cancer patients.

Activation of NK cells via the release of perforin and granzymes is important for inducing natural cytotoxicity [27]. Studies in perforin-deficient mice indicated that the cytotoxicity mediated by NK cells was greatly impaired [28]. The NK cells of mice with a deficiency in the GrzB cluster induce apoptosis in target cells more slowly than wild-type NK cells [29]. In this study, it was noticed that the levels of two anti-cancer molecules, perforin and granzyme B, were further increased after participants returned to the city, whereas the number of NK cells gradually decreased. It is difficult to determine the possible reason for this pattern. However, the result provides important insights into the enhancing effects of adjuvant anti-cancer therapy in combination with forest activities on natural cytotoxicity induced by NK cell activation when the numbers of NK cells decreased. Also, there is a possibility that cancer patients in the study were on an upward trajectory of recovery and all were getting better which could have accounted for the improvement in biomarker results.

It is noteworthy that breast cancer patients, who have significantly decreased natural cytotoxicity in peripheral blood [10,11], may have further immunosuppression after standard anti-cancer treatments, especially in NK cell activity [4–9]. For example,

Table 2
Change in outcome measures of NK cell population and levels of perforin and granzyme B between Day 1 in city and day 14 in forest, and day1 in city and day 21 in city.[a]

Outcomes	City[b]	Forest[c]	Return to City[c]	City vs. Forest		City vs. Return to City	
	(Day 1)	(Day 14)	(Day 21)	Mean difference (95% CI)	*P* value	Mean difference (95% CI)	*P* value
Number of NK cell (μl)	319.4 ± 129.3	444.6 ± 193.5	361.8 ± 149.9	125.3 (43.1 to 207.4)	<0.01	42.5 (−2.2 to 87.2)	0.06
Level of Perforin (pg/mL)	216.9 ± 151.2	344.9 ± 216.3	463.2 ± 298.3	128.1 (−28.4 to 284.5)	0.09	246.3 (53.7 to 438.8)	<0.02
Level of Granzyme B (pg/mL)	4.4 ± 6.6	11.2 ± 13.7	20.2 ± 19.4	6.7 (−2.8 to 16.3)	0.14	15.8 (3.1 to 28.4)	<0.02

[a] All changes are improvements. All values are means ± SD.
[b] Baseline measurement in the city before forest therapy on day 1.
[c] Follow-up measurement in the city after returning from the forest on day 21.

post-operative immunosuppression [8] and reduced NK cell activity [6] have been observed in patients who had undergone modified radical mastectomies. Additionally, suppression of NK cell anti-tumour activity was observed in patients undergoing routine chemotherapy [7,9] and radiotherapy [4,5]. Thus, an integrated approach is necessary, using current treatment regimens (optimal timing of surgery, optimal dosage of chemo- or radiotherapy to avoid immunosuppression) followed by adjuvant therapy that enhances immunoactivation. Here we showed the feasibility of this integrative approach.

The major limitation of this study was that the exact mechanism by which forest therapy induced NK cells to produce anti-cancer proteins is not clearly understood. However, an *in vitro* study indicated that volatile tree chemicals called phytoncides increase the activation of NK cells and intracellular anti-cancer molecules [20]. This indicates that wood fragrance may play an important role. This assertion is supported by several studies in animals [4,30] and humans [18] suggesting that fragrances from trees reverse stress-induced immunosuppression and normalise immune function and neuroendocrine hormone levels. However, the study results are limited because we did not measure volatile substances such as phytoncide or the chemical environment of the forest and compare the levels to those of the participants' normal living environments. The inclusion of such measurements and comparisons in future study designs could support the beneficial effects of the forest environment on various clinical conditions [21–26].

Additionally, the psychological benefits of staying in the forest than in the city, combined with the positive effects on human immunity, may also contribute to the effectiveness of forest therapy on the natural cytotoxicity demonstrated in this study [16,17,19]. In particular, the potential implications of ecopsychology or psychoneuroimmunology may support the mechanism by which forest therapy stimulates NK cells to produce anti-cancer molecules [31–33].

4.1. Methodological limitations

In the study, all subjects naturally interacted with other women with breast cancer in a forest environment. This social interaction with other people with the same medical condition may reduce the immunosuppression [4–9] observed after standard anti-cancer therapy, as poorer personal relationships appear to be related with immunological down-regulation [32,33]. However, this study did not evaluate the social interaction of the subjects. Any immunological improvement may have been due to social support of the other women, rather than the forest environment; further trials controlling for social interaction should be conducted. The other limitations of the study include that we did not collect data that could affect psychoneuroimmunology such as the daily psychological status, or sleeping conditions, or social interaction of the subjects in the forest [34]. In the study, results were limited in their power to confirm the clinical effects of forest therapy for breast cancer patients because of the small sample size used. However, the results indicate the necessity for a well-designed, adequately powered definitive trial with a larger sample size. We did not consider using a placebo-treated control group or applying blinding since it would not have been ethical to use a sham therapy, neither would it have been possible to prevent the subjects from recognising the forest therapy in this pragmatic field setting. However, a waiting-list control group would be utilised in the future definitive trial, as it is unclear if the results achieved are due to the forest therapy or other factors, *e.g.* natural improvement in the women's conditions post cancer treatment.

5. Conclusion

We have shown the feasibility of forest therapy as an adjuvant anti-cancer therapy to enhance NK cell activation, leading to the production of two anti-cancer molecules, perforin and granzyme B, in breast cancer patients who had received standard anti-cancer treatments. A definitive trial with a waiting list control should be performed with a larger sample size and long-term follow-up periods to confirm the feasibility and support this as an evidence-based treatment option for breast cancer patients. Further knowledge of the mechanism of immunoactivation by adjuvant forest therapy will support the development of various anti-cancer treatment strategies.

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Conflict of interest

The authors declare no conflicts of interest.

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