Does nature affect human immune function?

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What are natural environments (green spaces)?

- There are numerous definitions of natural environments (also called green spaces).
- The Centres for Disease Control define them as “open, undeveloped land with natural vegetation”; parks, forests, playing fields, river corridors and the like.
- Nature is defined as ‘the environment in which organisms or their biotopes expressly manifest themselves. In addition to nature reserves, this also includes farmland, production forest, urban green spaces and back gardens’ (Health Council of the Netherlands, 2004).
What is a forest?

- In 2000, the Forest Resources Assessment (FRA) 2000 project defined the “forest” as follows:
  - Forest includes natural forests and forest plantations.
  - It is used to refer to land with a tree canopy cover of more than 10 percent and area of more than 0.5 ha (hectare).
  - Forests are determined both by the presence of trees and the absence of other predominant land uses.
  - The trees should be able to reach a minimum height of 5 m.

What is a forest in Japan?

- In Japan, forest is used to refer to land with a tree canopy cover of more than 30 percent and area of more than 0.3 ha (hectare).
- The trees should be able to reach a minimum height of 5 m with a width of more than 20 m.

http://www.env.go.jp/earth/ondanka/santei_k/18_02/mat02_1.pdf
Why do people love (like) forests?

- The forest environment has been enjoyed by humans for a long time because of:
  - The quiet atmosphere
  - The beautiful scenery
  - The mild climate
  - The clean fresh air in the forest.
What is a forest bathing trip (Shinrin-yoku)?

- A forest bathing trip is a short leisurely trip visiting a forest, called "Shinrinyoku" in Japanese, which is similar to a natural aromatherapy.
- The purpose of forest bathing trip is relaxation and recreation by breathing in volatile substances from trees, called **phytoncides**, such as alpha-pinene and limonene.
Forest bathing trips (Shinrin-yoku) in Japan

- Incorporating forest bathing trips into a good lifestyle was first proposed in 1982 by the Forest Agency of Japan, and the first kick off meeting was held at Akasawa in Nagano prefecture located in northwestern Japan.

- Now it has become a useful and popular relaxation and stress management activity in Japan.
Forest environment and Immune function

- It is well known that immune system including natural killer (NK) cells plays an important role in defense against bacteria, viruses and tumors.
- It is also well known that stress inhibits immune function.
- Forest environment may reduce stress.
- Therefore, we speculate that forest environment may have beneficial effect on immune function by reducing stress.
Natural killer (NK)

Blood
↓
Red blood cells  White blood cells  platelet
↓
Granulocytes  Lymphocytes
↓
T cells  NK cells  B cells
(Immune cells)
Relationship between incidence rate of cancer and NK activity

Kazue Imai, et al.

Subjects: 3625
Periods of follow-up: 11 years

People with lower NK activity

People with higher NK activity

Males

Females
Mechanism of NK-induced apoptosis

(Tumor cell)

Ca^{++}↑, K^{+}↓, AIF, Cyto-C release

Apoptosis
Cancers and NK cells

Cancer cells → Criminals

NK cells → Policemen

Policemen >>> Criminals → Safe/peace

NK cells >>> Cancers → Health

Criminals >>> Policemen → Insecurity

Cancer cells >>> NK cells → Cancer
Today’s topics

1. Effect of 2-night/3-day trips to forest parks on human immune function
2. Effect of a day trip to a forest park on human immune function
Objective

To investigate the effect of the forest environment on human immune function, we investigated NK (natural killer) activity, the numbers of NK cells, and intracellular levels of anti-cancer proteins such as perforin, granzyme and granulysin in human lymphocytes during visiting to forest fields.
Subjects and schedule

1. **Subjects:** ① and ② 12 healthy male subjects aged 37-55 years (mean 43.1±6.1), ③ 13 healthy female nurses, aged 25-43 years (mean 28.8±4.6).
2. **Schedule:** Three-day/two-night trips in the beginning of Sept. at 3 different forest fields.
3. **On day 1,** subjects departed to forest fields in the morning, then walked for 2.5km during 2hs in the afternoon at a forest field.
4. **On day 2,** subjects walked for 2.5km during 2hs in the morning and afternoon, respectively at two different forest fields.
5. **On day 3,** the subjects finished the trip and returned to Tokyo after blood was drawn and a questionnaire survey was completed.
Subjects were walking in a forest
(Japanese oak, Japanese white birch, Bamboo grass)
Japanese cypress
Blood samples were taken at 8:00 am in all experiments.

Working day: Before the trip at 8:00 am
Day 2 of the trip at 8:00 am
Day 3 of the trip at 8:00 am
Day 7 after the trip at 8:00 am
Day 30 after the trip at 8:00 am
Parameters

- NK activity, number of NK cells,
- Intracellular Perforin, Granulysin, Granzymes A&B
- Estrogen, progesterone in blood
- Adrenaline and noradrenaline in urine (stress hormones)
- POMS (Profile of Mood States)
- Sleeping hours
- Physical activity
- Questionnaire for stress
A forest visit significantly enhances human NK activity in males.

Effect of a forest bath trip on human NK activity

* : p<0.05, ** : p<0.01, from before the trip #: p<0.05 from Day 1

Forest visits increased NK activity and this effect lasted for more than 7 days in both males and females.

*: p<0.05, **: p<0.01, from before the trip

A trip to a place without forest does not enhance human NK activity in males

Question

Q: Why do forest visits increase human NK activity?

A1: The number of NK cells increased. ↑
A2: The intracellular anti-cancer proteins increased. ↑
Forest visit significantly increased the number of NK cells in males.

Before the trip  | 1 day after trip  | 7 days after trip
---|---|---
62.56%  | 51.61%  | 48.87%
1.49%  | 2.01%  | 1.73%

In this subject, the NK cells increased from 28.27% to 39.22% on day 1 and 39.80% on day 7 after the trip.

Forest visit significantly increased the number of NK cells in males

****: p<0.01, significantly different from before the trip, #: p<0.01 significantly different from Day 1

Forest visits increased NK cells and this effect lasted for more than 7 days in both males and females.

Male

Female

*: p<0.05, **: p<0.01, from before the trip

A forest visit significantly increased granulysin, perforin, granzyme A/B-expressing lymphocytes

**: p<0.01, from before the trip $: p<0.01$ from Day 1

Forest visits increased intracellular anti-cancer proteins and this effect lasted for more than 7 days in both males and females.

*: p<0.05, **: p<0.01, from before the trip

Factors affecting NK activity and the countermeasures

- **Circadian rhythm** → Taking blood samples at the same time
- **Physical activity** → Setting it at the same level
- **Alcohol drinking** → Abstaining from drinking (During the experiment)
- **Estrogen, progesterone** → Measuring it
A forest visit decreased urinary adrenaline, whereas a city tourist trip did not affect this.

*: $p<0.05$ from Before

A forest visit decreased urinary adrenaline and noradrenaline in females

**p<0.01**

Forest bathing trips reduce the scores of anxiety, depression, anger, fatigue and confusion, whereas increase the score of vigor.

**Li Q. et al., Jpn J Hyg. 63 (2), 412, 2008**

**:** p<0.01 significantly different from before
Stress and immune response

Stressor

Forest
↓
Reducing stress
↓
Recover NK activity
↓
NK activity increased

Tension/ Anxiety

Disturbance of autonomic nerves

Release of Stress hormones

(Stress response)

Stress response

Stress hormones

Immune function

↓
NK activity increased
It is not clear whether a day trip to a forest park also increases human NK activity.

In the present study, we addressed this question.
A day trip to a forest park

1. **Subjects:** 12 healthy male subjects aged 34-53 years (mean 44.2±6.0).
2. **Schedule:** A day trip in the end of July to a forest park at Saitama prefecture located in the north of Tokyo, Japan.
3. The subjects walked for two hours each in the morning and afternoon for total of about 4 km in the forest park, and then returned to Tokyo.
4. A questionnaire of the Profile of Mood States (POMS) test was conducted before, during and after the walking.
5. Blood was sampled on the second day and on day 7 after the trip, and 6 days prior to the trip as a control.
A day trip to a forest park
A day trip to a forest park increases human natural killer (NK) activity and NK cells

Effect of a day trip to a forest park on Granzyme A-expressing cells in lymphocytes

In this subject, the total of Granzyme A-expressing cells increased from 27.07% (18.49+8.58) to 41.30% (24.85+16.45) after the trip.

A day trip to a forest park increases the expression of anti-cancer proteins in lymphocytes

**Perforin**  **Granzyme A**  **Granzyme B**  **Granulysin**

A  **B**  **C**  **D**

**Before**  **Day 2**  **Day 7**  **Before**  **Day 2**  **Day 7**  **Before**  **Day 2**  **Day 7**  **Before**  **Day 2**  **Day 7**

**Per-expressing cells (%)**  **GrA-expressing cells (%)**  **GrB-expressing cells (%)**  **GRN-expressing cells (%)**

****: p<0.01

A day trip to a forest park reduces cortisol in serum

Concentration of volatile substances (phytoncides) in the air of the forest park, calculated as $\alpha$-pinene (ng/m$^3$)

<table>
<thead>
<tr>
<th>Kind of phytoncides</th>
<th>Quercus serrata forest area</th>
<th>Pine forest area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoprene</td>
<td>5291.6</td>
<td>9.8</td>
</tr>
<tr>
<td>Tricyclene</td>
<td>15.1</td>
<td>18.1</td>
</tr>
<tr>
<td>$\alpha$-Pinene</td>
<td>70.0</td>
<td>241.1</td>
</tr>
<tr>
<td>Camphene</td>
<td>12.4</td>
<td>20.3</td>
</tr>
<tr>
<td>$\beta$-Pinene</td>
<td>18.8</td>
<td>39.8</td>
</tr>
<tr>
<td>D-Limonene</td>
<td>10.9</td>
<td>22.2</td>
</tr>
<tr>
<td>Bornyl acetate</td>
<td>0.0</td>
<td>11.1</td>
</tr>
</tbody>
</table>

The concentration of phytoncides represents the mean concentrations of each chemical between 9:30 am and 15:30 pm with consecutive sampling.
Mechanism of forest bathing-induced NK activity

Forest bathing → Reduce Stress

GrA, GrB → Granzymes → Perforin → Granulysin

Ca\(^{++}\)↑, K\(^{+}\)↓, AIF, Cyto-C release

(Apoptosis (cell death) → NK activity)
Conclusions

1. Forest visits significantly increase human NK activity in both males and females, which was mediated by increases in the number of NK cells and the intracellular anti-cancer proteins.

2. This effect lasted for more than 7 days, even 30 days after the trips.

→ Preventive effect on cancers?

3. Forest visits also significantly reduce the levels of urinary adrenaline and noradrenaline, which are stress hormones.

→ Stress management

4. Phytoncides from forests and relaxation may contribute to this effect.
Other effects

1. Forest visits significantly reduce blood pressure and blood glucose.

→preventive effects on hypertension, diabetes, and metabolic syndrome?

2. Forest visits stabilize the activity of autonomic nerves by increasing the activity of parasympathetic nerves and decreasing the activity of sympathetic nerves.

3. Forest visits reduce the scores of anxiety, depression, anger, fatigue and confusion, whereas increase the score of vigor.

→preventive effects on depression?
Fuji TV (News Speak) reported our research on forest medicine on November 8, 2005
The Japan Times reported our research on forest medicine on 2008.5.2

Friday, May 2, 2008

'Forest therapy' taking root
Researchers find that a simple stroll among trees has real benefits

By AKEMI NAKAMURA
Staff writer

For stressed-out workers, this may someday be a doctor's prescription: Walk around in the woods.

http://search.japantimes.co.jp/cgi-bin/nn20080502f1.html
An interview from Bloomberg TV
July 1, 2009
The New York Times Reported our research on forest medicine on July 5, 2010.


This time of year, allergies and the promise of air-conditioning tend to drive people indoors. But for those who can take the heat and cope with the pollen, spending more time in nature might have some surprising health benefits. In a series of studies, scientists found that when people swap their concrete confines for a few hours in more natural surroundings — forests, parks and other places with plenty of trees — they experience increased immune function.

Stress reduction is one factor. But scientists also chalk it up to phytoncides, the airborne chemicals that plants emit to protect them from rotting and insects and which also seem to benefit humans.

One study published in January included data on 280 healthy people in Japan, where visiting nature parks for therapeutic effect has become a popular practice called “Shinrin-yoku,” or “forest bathing.” On one day, some people were instructed to walk through a forest or wooded area for a few hours, while others walked through a city area. On the second day, they traded places. The scientists found that being among plants produced “lower concentrations of cortisol, lower pulse rate, and lower blood pressure,” among other things.

A number of other studies have shown that visiting parks and forests seems to raise levels of white blood cells, including one in 2007 in which men who took two-hour walks in a forest over two days had a 50-percent spike in levels of natural killer cells. And another found an increase in white blood cells that lasted a week in women exposed to phytoncides in forest air.

THE BOTTOM LINE

According to studies, exposure to plants and trees seems to benefit health.

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Forest bathing enhances human natural killer activity and expression of anti-cancer proteins.


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Abstract

In order to explore the effect of forest bathing on human immune function, we investigated natural killer (NK) activity; the number of NK cells, and perforin, granzymes and granulysin-expression in peripheral blood lymphocytes (PBL) during a visit to forest fields. Twelve healthy male subjects, age 37-55 years, were selected with informed consent from three large companies in Tokyo, Japan. The subjects experienced a three-day/two-night trip in three different forest fields. On the first day, subjects walked for two hours in the afternoon in a forest field; and on the second day, they walked for two hours in the morning and afternoon, respectively, in two different forest fields. Blood was sampled on the second and third days, and NK activity; proportions of NK, T cells, granulysin, perforin, and granzymes A/B-expressing cells in PBL were measured. Similar measurements were made before the trip on a normal working day as the control. Almost all of the subjects (11/12) showed higher NK activity after the trip (about 50 percent increased) compared with before. There are significant differences both before and after the trip and between days 1 and 2 in NK activity. The forest bathing trip also significantly increased the numbers of NK, perforin, granulysin, and granzymes A/B-expressing cells. Taken together, these findings indicate that a forest bathing trip can increase NK activity, and that this effect at least partially mediated by increasing the number of NK cells and by the induction of intracellular anti-cancer proteins.
A forest bathing trip increases human natural killer activity and expression of anti-cancer proteins in female subjects.

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Abstract

We previously reported that forest bathing trips enhanced human NK activity, number of NK cells, and intracellular anti-cancer proteins in lymphocytes, and that the increased NK activity lasted for more than 7 days after the trip in male subjects. In the present study, we investigated the effect of forest bathing trip on human NK activity in female subjects. Thirteen healthy nurses, age 25-43 years, professional career 4-18 years, were selected with informed consent. The subjects experienced a three-day/two-night trip to forest fields. On day 1, the subjects walked for two hours in the afternoon in a forest field; on day 2, they walked for two hours each in the morning and afternoon in two different forest fields; and on day 3, the subjects finished the trip and returned to Tokyo after drawing blood and completing a questionnaire. Blood and urine were sampled on the second and third days during the trip, and on days 7 and 30 after the trip. NK activity, numbers of NK and T cells, and granulysin, perforin, and granzymes A/B-expressing lymphocytes in the blood samples, the concentrations of estradiol and progesterone in serum, and the concentrations of adrenaline and noradrenaline in urine were measured. Similar control measurements were made before the trip on a normal working day. The concentrations of phytoncides in the forests were measured. The forest bathing trip significantly increased NK activity and the numbers of NK, perforin, granulysin, and granzymes A/B-expressing lymphocytes in the blood samples, the concentrations of estradiol and progesterone in serum, and the concentrations of adrenaline and noradrenaline in urine were measured. Similar control measurements were made before the trip on a normal working day. The concentrations of phytoncides in the forests were measured. The forest bathing trip significantly increased NK activity and the numbers of NK, perforin, granulysin, and granzymes A/B-expressing cells and significantly decreased the percentage of T cells, and the concentrations of adrenaline and noradrenaline in urine. The increased NK activity lasted for more than 7 days after the trip. Phytoncides, such as alpha-pinene and beta-pinene were detected in forest air. These findings indicate that a forest bathing trip also increased NK activity, number of NK cells, and levels of intracellular anti-cancer proteins in female subjects, and that this effect lasted at least 7 days after the trip. Phytoncides released from trees and decreased stress hormone levels may partially contribute to the increased NK activity.
References


5. Li Q et al. Relationships between percentage of forest coverage and standardized mortality ratios (SMR) of cancers in all prefectures in Japan. The Open Public Health Journal 2008; 1, 1-7.


