Natural Killer Cells and Exercise Training in the Elderly: A Review

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Abstract/Résumé
Consistent reports of the positive relationship between regular physical activity and immunosenescence have generated much excitement in the field of exercise immunology. It is generally accepted that natural killer (NK) cell activity per NK cell decreases with age; decreases in NKCA have been associated with infection and death in the aged. The effects of exercise and training on natural killer cells, components of the innate immune system, have been studied extensively in young people. However, the published research on the elderly population is limited. Generally it has been found that training increases or does not change natural killer cell activity or counts in the elderly. The clinical relevance of these results is yet to be fully explored. In addition, the limitations of these studies on immune function have been many, and studies are often difficult to compare due to differences in their methods and presentation of results.

La relation positive entre la pratique régulière d’activité physique et l’immunosénescence suscite un engouement marqué dans le domaine de l’immunologie de l’exercice. Il est généralement admis que l’activité des cellules NK diminue avec l’âge, et on associe cette déperdition aux infections et au décès. Les effets de l’exercice et de l’entraînement sur les cellules NK, constituantes du système immunitaire à la naissance, ont fait l’objet de beaucoup d’études chez de jeunes sujets. Malgré le peu d’études chez les personnes âgées, il en ressort

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Numerous studies indicate that participation in regular physical activity contributes to healthy aging, including increased functional capacities and independence. Endurance training helps maintain and improve cardiovascular health while strength/resistance training helps maintain and increase muscle mass (Kraemer et al., 1998; Mazzeo et al., 1998). Physical activity has also been shown to counter immunosenescence, an age-related decline in immune function. Several recent reviews have discussed the overall relationships between exercise, immune function, and aging (Bruunsgaard and Pedersen, 2000; Pedersen and Hoffman-Goetz, 2000; Woods et al., 2002).

An important component of the innate immune system, natural killer (NK) cells were named for their nonspecific cytotoxicity directed against tumor cells and virus-infected cells (Chiorean and Miller, 2001; Cooper et al., 2001). Research on the effects of training on NK cell activity and cell counts in the elderly has been limited. Therefore, the purpose of this review is to highlight the effects of resistance and endurance training on NK cell number and cytotoxic activity in the elderly population. The biology and effects of aging on NK cells are discussed first, followed by reviews of specific studies addressing natural killer cells, exercise, and aging. Finally, the role of modulators of NK cell activity and numbers such as catecholamines and cortisol during acute exercise and/or training will be explored.

**Biology of NK Cells**

Natural killer cells make up 10 to 20% of the peripheral blood human lymphocyte population (Chiorean and Miller, 2001; Miller, 2002). They are derived from lymphoid stem cells, as are progenitor T and B cells, members of the adaptive immune response. However, NK cells do not express the same cell surface proteins as their fellow T-lymphocytes (i.e., CD3, TCR). Cell surface receptor proteins, known as clusters of differentiation (CD), are recognizable through the use of monoclonal antibodies, allowing NK cells and their subsets to be defined by their CD expression patterns (Chiorean and Miller, 2001; Miller, 2002).

CD56, an isoform of the neural cell adhesion molecule (NCAM), is present on all NK cells (Chiorean and Miller, 2001; Miller, 2002). This surface antigen has no known function and is not involved in their cytotoxicity. Some 10% of NK cells express high densities of this surface antigen and are termed CD56 bright NK cells. This form of NK cell lacks CD16 (CD16−) and has low cytotoxic activity, yet shows high levels of proliferation. CD16 or FcRγIII is the natural killer cell Fc (crystallizing fragment) receptor, which plays a role in antibody-dependent cell cytotoxicity (ADCC) (Solana and Mariani, 2000). The remaining 90% of NK cells express low densities of the CD56 antigen and are termed CD56 dim NK cells (Cooper et al., 2001; Farag et al., 2002; Miller, 2002). CD16 (FcRγIII) is present...
on these CD56^bright NK cells, and this identifies them as the most mature and more cytotoxic NK cell subset. CD56^bright/CD16^- cells may be the precursor to the mature CD56^dim/CD16^- cells (Chiorean and Miller, 2001; Miller, 2002). Other relevant NK cell surface proteins include CD7, CD2, and CD8. All NK cells express CD7, and most CD56^bright cells express CD2.

In contrast, 20% of CD56^dim NK cells do not express CD2 antigens (Miller, 2002). These CD56^dim/CD2^- have been found to have lower cytotoxicity compared to their CD2^+ counterparts. CD8, a surface protein marker for cytotoxic T-lymphocytes, is also found on 20 to 40% of CD56^dim NK cells (Miller, 2002). The expression pattern of CD3^-CD16^-CD56^+ is now most commonly used to identify natural killer cells. However, in the past it was common to use single surface markers to identify NK cells (Rowbottom and Green, 2000).

NK cells are the first line of defense against viral infection, controlling viral replication until cytotoxic T-progenitor cells have had time to activate, proliferate, and differentiate into functional cytotoxic T-lymphocytes (CTLs). In contrast to CTLs, NK cell lysis occurs within hours of first-time target cell exposure. NK cell attack does not require expression of self-major histocompatibility complex (self-MHC) on the target cell, and NK cells do not use antigen-specific receptors for target recognition (Chiorean and Miller, 2001). Each NK cell expresses an assortment of inhibitory and activating receptors that regulate its cytotoxicity (Farag et al., 2002). Three receptors have recently been identified and characterized. They have been termed natural cytotoxicity receptors (NCR) and are the most accurate surface markers for the identification of NK cells (Moretta et al., 2001a; 2001b; Ryan et al., 2001).

Activity of NK cells is stimulated by interferons IFN-α and IFN-β, and interleukins IL-2, IL-12, IL-15, and IL-21. This stimulation results in increased NK cell proliferation and increased cytokine secretion (Chiorean and Miller, 2001). NK cells secrete tumor necrosis factor (TNF), IFN-γ, IL-1, IL-5, IL-8, and IL-10 (Chiorean and Miller, 2001; Miller, 2002). These cytokines play important roles in the two killing mechanisms used by NK cells. The first mechanism involves an exocytosis pathway in which NK cell perforins induce pore formation in the target cell membrane, allowing granzymes to enter and induce apoptosis of the target cell. The second mechanism involves the TRAIL (TNF-related apoptosis-inducing-ligand) pathway that also leads to apoptosis of the target cell (Chiorean and Miller, 2001).

**NK Cell Number and Function**

Natural killer cytotoxicity or natural killer cell activity (NKCA) is generally assessed using a standard Chromium-release (Cr-release) assay with K562 tumor cells as targets. The assay measures the degree of cytotoxic killing by the release of radio-labeled chromium from the target cells (Rowbottom and Green, 2000). Most laboratories use isolated peripheral blood mononuclear cells (PBMC) for this assay although whole blood is also used. It has been suggested that the whole-blood technique is a better representation of the in-vivo environment than the traditional PBMC isolation method (Braun et al., 1999). Cytotoxicity values are most often reported as either % cytotoxicity or as lytic units. Percent cytotoxicity can be
expressed per NK cell (lytic index) or per fixed number of target cells at different effector-target ratios (Baron et al., 1985; Kutza et al., 1995; Miles et al., 2002b). Normal resting % cytotoxicity values tend to range from approximately 20 to 50% (Kutza et al., 1995). However, Kmiec and associates (2001) defined low NKCA as below 20% cytotoxicity and high NKCA as above 20% cytotoxicity (at an effector-target ratio of 25:1) for elderly populations after observing the NKCA of more than 600 elderly persons.

Lytic units (LU) were developed to standardize cytotoxicity values in order to make the comparisons between laboratories more efficient and valid (Bryant et al., 1992; Pross et al., 1981). Whiteside and colleagues (1990) reported that NKCA in the peripheral blood of healthy adults ranged from 50 to 302 LU, with a median of 132 LU. Studies frequently use one method of reporting or the other, which makes direct comparison of the level of agreement between them difficult. Some indication that there is a lack of agreement between % cytotoxicity and the activity calculated by lytic unit is seen in Ogata et al. (1997), who reported that NK activity on a per-cell basis correlated negatively with age, while this was not the case for LU values. While the reliability of the lytic unit has been questioned (Dye et al., 1991), it continues to be used as a standard measure of NK activity by many researchers, and both methods of presentation are in common use.

Natural killer cell counts are another approach used to quantify natural killer cells. Generally, flow cytometry is used to identify NK subsets expressing CD16 and/or CD56, and it is now internationally accepted to use the expression of CD3–CD16+CD56+ to identify NK cells (Rowbottom and Green, 2000). Absolute NK counts, NK cells as a proportion of total lymphocyte populations, or NK cells as a proportion of total PBMC are most often reported. Reporting both counts and NKCA allows for the relationship between the cell counts and activity to be assessed as well.

The relationship between NK cell counts and NK cell cytotoxicity during acute exercise is controversial. For the most part it is accepted that NK cell counts and cytotoxicity both increase during and immediately following an acute bout of exercise. Most authors attribute the increase in cytotoxicity to the increase in and redistribution of NK cell subsets that are recruited from the spleen, lungs, and other tissue reservoirs during exercise (Braun et al., 1999; Hoffman-Goetz, 1998; Woods et al., 1999b). In addition, during recovery a suppression of NKCA is usually observed. There have been two proposed explanations for this suppression. The first is a prostaglandin-induced suppression of NKCA while the second explanation deals with a numerical redistribution of NK cells. Both explanations have been supported by several studies (Braun et al., 1999; Nieman et al., 1993b).

**NK Cells and Aging**

Reports consistently show that the aging process impairs certain parameters of immune function (Kostka et al., 2000; Solana and Mariani, 2000). It has been shown that patients with decreased, weak, or a lack of NK cell function are more susceptible to viral infections, especially those caused by the herpes simplex virus (HSV), Epstein-Barr virus (EBV), and human cytomegalovirus (HCMV) (Biron et al., 1989; 1999). A recent study demonstrated an association between low NK cell activity and increased risk of infection in the elderly, with low NKCA also
being linked to reduced survival from infection (Ogata et al., 2001). Therefore, preserving NK cell function in the elderly is important as this age group is more susceptible to infectious diseases, autoimmune disorders, and malignancy (Fahlman et al., 2000; Kostka et al., 2000; Ogata et al., 1997). Ogata and colleagues (1997) found that NK cell activity per NK cell decreased with age and that in a group of 52 elderly hospitalized patients the decrease was related to the incidence of severe infection or death due to infection. They later confirmed this finding with another study which concluded that low NKCA is associated with development of infection and death due to infection in elderly people (Ogata et al., 2001).

Centenarians have provided much insight into the role of NK cells in healthy aging. For the most part, it has been found that centenarians have an increased proportion of NK cells (Franceschi et al., 1995; Miyaji et al., 1997), and increased IFN-\(\gamma\) production by NK cells following activation with PMA and the calcium ionophore A23187 (Miyaji et al., 2000). Despite this increase, it has been found that their overall NK cell function is lower compared with younger controls (Miyaji et al., 1997). Miyaji and colleagues (1997) studied both healthy and unhealthy centenarians. There was a tendency for the healthy independent centenarians to have a higher number of NK cells compared to the unhealthy group. However, NK cell activity decreased independent of health status. It was concluded that the increase in cell number was a compensation for decreased NK cell activity, an observation supported by other recent studies (Solana and Mariani, 2000).

However, studies of noncentenarian elderly have revealed different patterns of change with age. For example, Kutza and Murasko (1994) found an increase in resting NKCA of 43 elderly individuals ages 65 to 100 years, when compared to 21 young subjects ages 23 to 35 years. In addition, they reported no difference in the percentage of CD56\(^+\) cells between the young and old groups. There was no correlation between the percentage of CD56\(^+\) cells and cytotoxicity in the elderly. Kutza and Murasko concluded that the observed increase in cytotoxicity must be due to an increase in activity per NK cell, in contrast to the findings in healthy centenarians (Franceschi et al., 1995; Miyaji et al., 1997).

Other studies have shown that resting NK cell cytotoxicity is unaffected by the aging process (Kutza et al., 1995; Ligthart et al., 1989). For example, Ligthart and co-workers (1989) reported no change in NKCA per cell in the healthy aged. However, a single cell cytotoxicity assay was used in lieu of the standard Cr-release assay to determine NK cell activity. The single cell assay was developed by Grimm and Bonavida and is used to determine the ability of NK cells to bind to a target and kill it (Whiteside et al., 1990). Ligthart and colleagues (1989) acknowledged that direct comparison between the single cell assay and the Cr-release assay could not be done as they measure different parameters of NK activity. This study also reported that NK cell activity was directly proportional to NK cell numbers in peripheral blood.

In addition, a review by Kutza and colleagues (1995) concluded that NKCA does not change with age. Of the 31 studies reviewed, 15 used the standard Cr-release assay, with K562 target cells, PBMC effector cells, percent cytotoxicity as output, and a well-defined subject population. For the most part these 15 studies indicated that NKCA is preserved with age. However, 4 of the 15 studies did indicate an age-related change, with 2 reporting increases in NK activity with increas-
ing age and 2 reporting a decrease in NK activity with increasing age (Kutza et al., 1995). In addition, their review did not report the effects of age on NK cell numbers, an omission which renders comparisons with more recent studies reporting changes in NKCA on a per-NK-cell basis more difficult.

In terms of NK cell counts, McNerlan and associates (1998) reported higher total NK cell numbers in older subjects relative to young subjects. They examined different subsets of NK cells in 229 subjects from all age groups and reported increases in CD3−CD16+CD56+ cells with respect to both absolute number and percentage of lymphocytes in older subjects. Such increases in percentages of NK cells in PBMC of older persons has been confirmed in other studies (Di Lorenzo et al., 1999; Solana and Mariani, 2000; Woods et al., 1998).

Differences in NKCA per cell with age may reflect changes in the response of NK cells to stimuli. The cytokines IL-2 and IFN-α are mediators that can stimulate NK cytotoxic activity, and several studies have assessed their effects on the activity of NK cells from young vs. elderly subjects. Again, this has led to a variety of conclusions. IL-2-enhanced cytotoxicity has been reported to be unaffected by the aging process (Fiatarone et al., 1989; Kutza and Murasko, 1994). More recently it has been reported that TNF-α secretion and perforin content in response to IL-2 do not change with aging. However, IL-2 induced IFN-γ production has been found to be decreased in the elderly (Borrego et al., 1999; Solana and Mariani, 2000). On the other hand, IL-8 production has been reported to increase with IL-2 or IL-12 stimulation in the elderly. Nonetheless, the increase is significantly lower than that observed in younger persons. It was concluded in two studies on healthy subjects over the age of 90 years that the lower levels of IL-8 may contribute to the reduced cytotoxic activity per cell often reported (Mariani et al., 2001; 2002).

Responses to IFN-α are also interesting. Woods and colleagues (1998) reported that while IFN-α increased NKCA for both young and old subjects, NK cells from older subjects were less responsive to stimulation by IFN-α. In an earlier study, Kutza and Murasko (1994) showed that while stimulation with IFN-α concentrations of 100–500 U is equally effective for NK cells from young and elderly subjects, NK cells from the elderly are less responsive to lower IFN-α doses (10–50 U) than are NK cells from young persons. Their study not only found differences in responsiveness to low-dose IFN-α with age but also illustrated a reduced response to higher-dose IFN-α with age, suggesting that the overall profile of changes in cytokine-responsiveness with age may be quite complex.

Thus, the majority of studies completed to date have found that resting natural killer cell activity remains constant as healthy individuals age. However, it appears that there is an age-related increase in NK cell numbers. This supports the hypothesis that the activity per NK cell decreases with age. This hypothesis is supported by the studies on centenarians which conclude that the increase in NK cell numbers is to compensate for the decrease in NKCA per cell (Miyaji et al., 1997). However, more research is needed to validate this hypothesis.

**NK Cells, Elderly, and Strength/Resistance Training**

There have been only 4 studies to date on the effects of strength training (or resistance training) on immune function in the elderly. The longest resistance training
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intervention published lasted 6 months but did not study the effects on the elderly (Miles et al., 2002a). That study reported the effects of 6 months of resistance training on the immune function of women ages 18–30 years and is summarized in Table 1. It assigned 49 women to four groups based on body size and initial strength. The first two groups performed resistance training designed for strength and power for either the whole body or the upper body only. The second two groups completed resistance training designed for strength and hypertrophy for either the whole body or the upper body only. The study also included a control group that did not participate in either training group. Leukocyte and lymphocyte counts, as well as lymphocyte proliferation, were measured at baseline and at 3 months and 6 months into the exercise intervention. The study reported a transient increase in NK cell counts between the start of training and the 3rd month of training, but no significant increase overall. There were no other significant findings with respect to the other parameters studied (Miles et al., 2002a).

Rall and co-workers (1996) studied the effects of 12 weeks of resistance training on selected immune parameters in elderly individuals. They randomly assigned 14 healthy individuals between the ages of 65–80 years to a strength training (n = 8) or non-strength-training group (n = 6). Six healthy age-matched controls were included in the study as well. The resistance training was done twice weekly for 12 consecutive weeks. However, NK cell activity and/or numbers were not included in the immune parameters studied. Nonetheless, Rall et al. found that strength training did not alter any parameter of immune function in the 8 trained elderly individuals studied.

The remaining 3 resistance training studies included natural killer cytotoxicity and/or cell counts in their immune function measurements. Most recently, Bermon and colleagues (2001) studied the effects of a strength training program on the NK cell counts of 16 sedentary older individuals. The training involved resistance training 3 times a week for 8 weeks. Before and after completion of the training, blood samples were taken immediately and 6 hours following a standardized strength test. The testing protocol included 4 sets of 5 repetitions at 5 rep max, and 2 sets of 12 reps at 12 rep max, for the horizontal leg press, seated chest press, and bilateral leg extension. Prior to the strength training program, NK cell counts in the elderly decreased by 33% in response to the standardized strength test, a response essentially opposite from that seen with young control subjects. Conversely, after the training intervention, NK cell counts slightly increased (4.7% increase) in response to the same standardized strength test. This increase was nonsignificant; however, this finding illustrates that strength training can alter patterns of NK activity in older persons (Bermon et al., 2001).

Flynn and associates (1999) found that 10 weeks of resistance training did not improve selected parameters of immune function in older women (n = 29), ages 67–84 years, who were randomly assigned to either a resistance training group or a control group. The training group completed exercises focused on the lower extremities 3 times a week for 10 weeks. Blood samples were taken pre, post, and at 2 hours post resistance training (at baseline and 10 weeks). NK cell cytotoxicity increased immediately after exercise for both the control group and the exercise group at 10 weeks. However, NKCA was higher for the training group than the control group after acute exercise both before and after training. Prior to training,
Table 1  Effects of Training on NK Cells (Cytotoxicity and/or Counts) and Possible Exercise Training-Induced NK Cell Activity Modulators in Young Untrained Subjects

<table>
<thead>
<tr>
<th>Author &amp; Duration</th>
<th>Exercise Type &amp; Duration</th>
<th>No., Gender, Age (yrs)</th>
<th>Effect on NKCA Counts</th>
<th>VO$_{2\text{max}}$ (ml·kg$^{-1}$·min$^{-1}$)</th>
<th>Effects on Epinephrine, Norepinephrine, Cortisol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miles et al. (2002a)</td>
<td>6 months intense resistance training (4 programs)</td>
<td>16 F: total power 18 F: total body hypertro. 15 F: upper body power 15 F: upper body hypertro. 7 F: control</td>
<td>Increase in NK cell counts after 3 months for all exercise groups Returned to baseline after 6 months</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Takahara et al. (1999)</td>
<td>Treadmill jogging, 2 hrs/day 3 × week (50% VO$_{2\text{max}}$)</td>
<td>16 F (20–22) all untrained</td>
<td>Increased NKCA posttraining</td>
<td>Initial: 33.1 ± 3.4 Final: 38.3 ± 6.6 Significant increase</td>
<td>[Norepinephrine] increased after training; Incr. in norepinephrine &amp; epinephrine correlated w/ increase in VO$_{2\text{max}}$; Increase in NKCA correlated w/ increase in epinephrine</td>
</tr>
<tr>
<td>Rhind et al. (1996)</td>
<td>Cycle ergometry at 60% VO$<em>{2\text{max}}$ (60 min) after 12 wks of 65–70% VO$</em>{2\text{max}}$ cycle ergom. (30 min) 4–5 days/wk</td>
<td>9 M (25.3) exercise group 6 M (23.4) control</td>
<td>Increased number CD3$^+$CD16$^+$ and/or CD56$^+$ cells</td>
<td>Initial: 40.6 (2.8) Final: 49.2 (1.3) Significant increase</td>
<td>–</td>
</tr>
<tr>
<td>Nehlsen-Cannarella et al. (1991)</td>
<td>Brisk walking 45 min/day, 5 × week for 15 weeks</td>
<td>18 F (36.0) exercise group; 18 F (32.8) nonexercise group all untrained mildly obese</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Note: NKCA = natural killer cell activity; [Norepinephrine] = concentration of norepinephrine.
there was an increase in CD3−CD16+CD56+ numbers immediately post acute exercise, which later returned to baseline at 2 hrs post for the training group. It was concluded that a 10-week resistance training program did not alter resting or exercise-induced parameters of immune function in elderly women (Flynn et al., 1999). An additional issue addressed in this study was the potential for suppression of NK activity in the elderly following an acute bout of resistance exercise; however, this was found not to be the case for this group.

Finally, Rincon and co-workers (1996) found that NK cell cytotoxicity decreased in 6 frail elderly men who participated in a training program of increasing intensity 3 times a week for 3 months. Most of the program consisted of strength and balance exercises. Seven age-matched controls were used for comparison. Blood samples were taken at Weeks 1, 6, and 12. NKCA decreased following the training program; however, the decrease was not accompanied by changes in NK cell counts. Rincon et al. concluded that overexertion in the frail elderly may be of concern in terms of the potential impact on NKCA and their biological role in preventing metastasis.

Based on the results of these studies, it appears that resistance training has relatively minor effects on natural killer cell counts or activity in the elderly. However, it should be noted that only three relatively short studies have been completed to date, with the maximum duration of training being 12 weeks. Full exploration of the impact of long-term resistance training on the immune response in the elderly will require studies of longer duration and an examination of a broader range of immunological parameters.

**NK Cells, Elderly, and Endurance Training**

Several studies have examined other types of exercise training and the corresponding effects on immune function in the elderly. Once again, the longest intervention lasted 6 months while the majority lasted no longer than 12 to 16 weeks. Again, the conclusions from these studies vary in terms of the effects of exercise on natural killer cell cytotoxicity and number.

Woods and colleagues (1999a) demonstrated that NK cell cytotoxicity increased as a result of 6 months of moderate aerobic exercise in the elderly. They randomly assigned 29 previously sedentary elderly (65.3 ± 0.8 yrs) to an aerobic training group or a flexibility/toning control group. The aerobic exercise consisted of brisk walking 3 times a week over the 6-month period (approx. 40 min per session). The flexibility training group performed light resistance and stretching exercises in lieu of walking. An exhaustive treadmill test was undertaken before and after the training, and blood was drawn at this time (pre, post, and 20 min post). Prior to training, there were no differences between groups in NKCA or in the proportion of circulating CD56+ cells. NKCA increased at postintervention for the aerobic training group but presented little change in the flexibility training group. There was no change in percentage of CD56+ cells for either group after the training intervention (Woods et al., 1999a).

Fahlman and associates (2000) reported similar results in a study involving 15 healthy active elderly nuns who performed 10 weeks of endurance training. The training consisted of brisk walking (70% heart rate reserve) 3 times a week for
50 min. Fourteen nonexercising controls were also included in the study. Blood was drawn before and after 20 min of walking both pre- and posttraining. NKCA significantly increased over resting values in response to 20 min of walking, and this increase was seen both before and after the endurance training period. Resting NKCA of the control group showed a significant decrease at the end of the 10-week period. This decrease was attributed to seasonal variation; however, the decrease did not occur in the training group, and Fahlman et al. (2000) suggest that this exercise intervention counteracted a winter-associated decrease in cellular immune response. Surprisingly, the CD56+CD16+CD3− concentration decreased due to the training intervention for the training group and increased in the nontraining group. This study had a distinct advantage in that all participants lived together and exhibited similar eating, lifestyle, and exercise patterns.

These two studies confirmed an earlier one by Crist and co-workers (1989) in which 7 elderly women (age 72 ± 1 yr) participated in a 60-min exercise session involving treadmill exercise 3 times a week for 16 weeks. There were 7 age-matched nonexercising controls included as well. Blood samples were only taken after the training intervention, prior to and after 20 min of treadmill exercise. The exercise group had higher basal NKCA after the training intervention. In addition, both groups had increased NKCA after the acute treadmill exercise; however, only the trained group had significantly higher NK activity (57.8% vs. 37.8%). Similarly, in a murine study, Ferrandez and De la Fuente (1996) found that moderate training of older mice for 20 days increased NK cell activity significantly more than in sedentary aged controls.

Another study on the influence of long-term physical exercise on elderly women was done by Nieman and colleagues (1993a), who studied the effects of a 12-week aerobic training program on the immune function of 30 previously sedentary elderly women. The women were randomly assigned to either the experimental walking group (n = 14) or a calisthenics group (n = 16). Twelve high-fit age-matched controls and 13 young women (age 21.5 ± 0.5 yrs) were included in the study for comparison. Blood samples were taken from the 30 elderly women at rest (no exercise for at least 12 hrs) before and after the training interventions. Prior to the training, the high-fit elderly women had significantly higher baseline NKCA compared to the sedentary women. After training, there were no changes in basal NKCA for either the walking or calisthenics group. Thus it was concluded that the training programs did not alter NKCA in the elderly (Nieman et al., 1993a).

Shinkai and associates (1995) also found no significant differences between NK cell cytotoxicity of 17 older recreational runners (mean age 63.8 yrs), 19 sedentary elderly controls (mean age 65.8 yrs), and 16 young sedentary controls (mean age 23.6 yrs). All participants were male and no exercise was performed 36 hours prior to blood testing. The results of that study were confirmed by Yan and colleagues (2001), who tested the immune function of men ages 20–73 years who had participated in moderate exercise at least twice a week for more than 3 years. The participants were divided into three age groups: young (20–39 yrs), middle-aged (40–59 yrs), and elderly (60+ yrs). Sedentary age-matched control groups were also tested. Blood samples were taken at rest and the study reported an increased concentration of CD16+CD56+ cells in the 28 elderly participants compared to their age-matched controls and to the young group. In spite of this increase in cell
number, there were no significant differences in NKCA between groups (Yan et al., 2001).

Overall, the endurance training studies report either an increase in NKCA or no change in NKCA. It is important to note that it is the most recent studies (Fahlman et al., 2000; Woods et al., 1999a) that report increases in NKCA. This may reflect their choice of study population and exercise program design. Fahlman et al. (2000) examined the effects of 10 weeks of endurance training on active but nonexercising elderly women, and Woods et al. (1999a) looked at the impact of 6 months of exercise intervention with a population defined as “previously sedentary”; both studies used similar participant exclusion criteria, and both used brisk walking as a key part of the exercise regimen. These results are promising and may complement the other known benefits of endurance training such as increased cardiovascular fitness (Mazzeo et al., 1998).

**NK Cells, Elderly, and Acute Exercise**

The majority of studies have reported that acute exercise increases NK cell counts and activity in the aged. In a study conducted by Woods and associates (1999a), discussed in the previous section, elderly participants responded to acute exercise prior to an endurance training intervention (aerobic or flexibility/toning training) with an increase in NKCA. This increase in NKCA was also observed at post-intervention for both training groups. In addition, the percentage of CD56+ cells increased in both groups due to the acute exercise before and after the training intervention.

In an earlier study, Woods and associates (1998) reported the effects of a maximal treadmill test on NK cell counts and activity of both young and old subjects. Thirty three healthy elderly persons ages 58–77 and 14 healthy young controls ages 18–27 were tested. Prior to exercise, both groups had similar basal NKCA. However, the older group presented significantly higher NK cell numbers in their PBMC. The NKCA and percentages of NK cells in the PBMC increased for both groups in response to the treadmill exercise test. A correlation between basal NKCA and percentages of NK cells in the PBMC was found for the young control group but not for the elderly group (Woods et al., 1998).

These results confirm an earlier study by Fiatarone and co-workers (1989) in which 9 elderly and 8 young subjects were tested for changes in NKCA and NK cell counts after maximal exercise. The exercise test was a progressive cycle ergometer test, with the intensity increased by 20–30 Watts every 60 sec until exhaustion. Because the workload was adjusted based on the individual’s exercise ability, the duration and the maximum workload of the exercise test were similar between the young and old groups (10.6 ± 1.0 vs. 11.7 ± 0.9 min; 321 ± 55 vs. 271 ± 30 W). It was found that basal activity and counts were similar for both age groups; however, the older participants displayed a tendency for higher baseline measurements. In response to exercise, both groups had nonsignificant increases in NKCA and percentages of NK cells (Fiatarone et al., 1989).

Dohi et al. (2001) examined the effects of an acute bout of resistance exercise on immune function of young women and reported that NK cell counts significantly increased in both the lower and higher strength groups. Nieman and
<table>
<thead>
<tr>
<th>Author</th>
<th>Exercise Type (&amp; Duration)</th>
<th>No., Gender, Age (yrs)</th>
<th>Immediately Post-exercise Effect</th>
<th>Recovery Time</th>
<th>VO$_2$ max</th>
<th>Effects on Epinephrine, Norepinephrine, Cortisol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horn et al. (2002)</td>
<td>Cycle ergometry (4 × 4 min submax, 4 min max)</td>
<td>13 M (25) well-trained</td>
<td>Increased absolute count CD3$^+$CD16$^+$CD56$^+$ cells, no Δ in % CD94$^+$ cells</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Mitchell et al. (2002)</td>
<td>Cycle ergometry at 55% VO$_2$max (75 min)</td>
<td>10 M (19–23) moderately trained</td>
<td>NKCA and NK cell number increased</td>
<td>NKCA and NK cell no. below baseline (2 hr) returned to baseline (24 hr)</td>
<td>–</td>
<td>[Cortisol] decreased throughout until 2 hr post</td>
</tr>
<tr>
<td>Miles et al. (2002b)</td>
<td>Treadmill run at 80% VO$_2$max (60 min)</td>
<td>6 M (18–40) moderately trained (4 controls)</td>
<td>CD3$^+$CD16$^+$ cell concentration increase postexerc.; NKCA (expressed as % cytotoxicity) increased postexerc. No change in NKCA (expressed as LI)</td>
<td>CD3$^+$CD16$^+$ cell concentration decreased nonsignif. (1.5 hr); NKCA (expressed as % cytotoxicity) decreased nonsignificantly (1.5 hr)</td>
<td>55 ±2.9</td>
<td>–</td>
</tr>
<tr>
<td>Krzywkowski et al. (2001)</td>
<td>Cycle ergometry at 75% VO$_2$max (120 min)</td>
<td>10 M (37) healthy elite athletes</td>
<td>NKCA (expressed in % cytotoxicity and lytic units) and concentrations of NK cell subsets increased</td>
<td>NKCA decreased at E/T ratios of 25:1 and 50:1 (2 hr); Concentrations of NK cell subsets decreased below baseline (2 hr)</td>
<td>–</td>
<td>[Epinephrine] increased postexerc, slightly above baseline levels at 2 hr post; [Norepinephrine] increased postexercise, returned to baseline 2 hr post</td>
</tr>
<tr>
<td>Study</td>
<td>Exercise Protocol</td>
<td>Duration</td>
<td>NK Cell Activity</td>
<td>NKCA (% cytotoxicity)</td>
<td>Notes</td>
<td></td>
</tr>
<tr>
<td>---------------</td>
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<td></td>
</tr>
<tr>
<td>Braun et al.</td>
<td>Treadmill runs at 85.5% VO₂max (60 min)</td>
<td>10 M (36.0) well-trained</td>
<td>CD₃⁻CD₁₆⁺CD₅₆⁺ cell numbers &amp; NKCA (expressed as mean % cytotoxicity and lytic index using whole blood assay and PBMC assay) increased</td>
<td>NKCA (% cytotoxicity) decr. below baseline (1.5 hr) for whole blood assay; NKCA (% cytotoxicity) returned to baseline using PBMC assay; NKCA (lytic index) returned to baseline (1.5 hr) using whole blood assay</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tate et al.</td>
<td>Max cycle ergometer at pedal speed of 75 rpm</td>
<td>7 M (18–26) well-trained</td>
<td>NKCA increased postexercise</td>
<td>–</td>
<td>Serum [cortisol] increased postexercise</td>
<td></td>
</tr>
<tr>
<td>Nieman et al.</td>
<td>Sets of 10 parallel leg squats until muscular failure</td>
<td>10 M (46.9) trained (9+ yrs weightlifting)</td>
<td>CD₅₆⁺ cell count increased No change in NKCA</td>
<td>NKCA decreased below baseline (2 hr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nieman et al.</td>
<td>High (80% VO₂ max) vs. mod intensity (50% VO₂ max) treadmill exerc. (45 min)</td>
<td>10 M (22) well-conditioned</td>
<td>Increased % CD₃⁻CD₁₆⁺CD₅₆⁺ cells</td>
<td>% CD₃⁻CD₁₆⁺CD₅₆⁺ cells below baseline (1 hr–3.5 hr)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** NKCA = natural killer cell activity; [Epinephrine] = concentration of epinephrine; [Norepinephrine] = concentration of norepinephrine; [NE] = concentration of norepinephrine; [Cortisol] = concentration of cortisol; LI = lytic index.
associates (1995) studied the effects of acute resistance exercise on immune function in young men. They too reported a significant increase in NK cell (CD56+) counts postexercise. However, the cell numbers decreased to below baseline 2 hours later. In addition, Nieman et al. (1995) reported no change in NKCA immediately postexercise, but a significant decrease in measured NKCA at 2 hours post exercise.

The majority of studies have found that acute exercise increases NKCA and NK cell counts in the elderly. Effects of both resistance and aerobic exercises have been studied to date. Interestingly, the increases observed in responses of elderly persons to acute exercise in these studies are consistent with the results of acute exercise conducted on younger participants (see Tables 2 and 3). The latter are discussed in the next section.

**NK Cells and Exercise in Young Persons**

While this review concentrates on the effects of different types of exercise on immune function in the elderly, it is important to note the research that has been done with younger subjects. Many studies have addressed the effects of acute exercise on NK cell number and activity in both trained and untrained young subjects. Shephard and Shek (1999) published a meta-analysis on the effects of exercise and training on NK cell counts and activity. The results of several key studies completed since this meta-analysis are presented in Tables 2 and 3. Generally, an immediate postexercise increase in NK cell activity, number, and/or proportion (of total lymphocytes or PBMC) has been observed, followed by a decrease below baseline levels within 2 hours. Fewer studies have examined the effects of training on NK cells, although those that have suggest an increase in NKCA or NK cell counts. Results of recent studies in this area of research are presented in Table 1.

**Exercise-Induced NKCA Modulation**

Large numbers of β-adrenoceptors are found on NK cells, and it has been reported that catecholamines affect the adhesion of NK cells to endothelial cells (Jonsdottir, 2000b). Thus, increased levels of epinephrine and norepinephrine are thought to be responsible for the recruitment of lymphocytes during acute exercise (Bruunsgaard and Pedersen, 2000; Jonsdottir, 2000a). In addition, catecholamines and cortisol have been shown to play a role in modulating a variety of exercise-induced changes in immune function (Flynn et al., 1999; Mazzeo, 1994). It has also been reported that catecholamines may play a role in increasing the cytotoxic activity of NK cells (Jonsdottir, 2000b). Hormonal responses to exercise tend to diminish with training, while basal levels tend to remain unchanged and may be of minimal physiological significance.

Very few of the studies of training effects on NK cells have reported levels of catecholamines or cortisol in the plasma or serum. Table 1 shows only one study on younger subjects (Takahara et al., 1999) in which NKCA, epinephrine, and norepinephrine were all observed to increase. In addition, that study found a positive correlation between NKCA and epinephrine. It is not surprising then that few studies examining the impact of training on natural killer cells in the context of
Table 3 Effects of Acute Exercise on NK Cells (Cytotoxicity and/or Counts) and Possible Natural Killer Cell Activity Modulators in Young Untrained Subjects

<table>
<thead>
<tr>
<th>Author</th>
<th>Exercise Type &amp; Duration</th>
<th>No., Gender, Age (yrs)</th>
<th>Immed. Post-exerc. Effect</th>
<th>Recovery Time</th>
<th>VO₂ max</th>
<th>Effects on Epinephrine, Norepinephrine, Cortisol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dohi et al. (2001)</td>
<td>6 sets of 10 RM (2 min rest)</td>
<td>8 F (22.5) low strength; 8 F (22.5) high strength</td>
<td>Increase in NK cell counts for both groups</td>
<td>–</td>
<td>–</td>
<td>High strength group: strong trend for increase in [cortisol]; No change in [cortisol] for low strength group</td>
</tr>
<tr>
<td>Strasner et al. (1997)</td>
<td>Cycle ergometry at 80%, 40%, 0% VO₂max (25 min each)</td>
<td>8 F (24.8) using oral contraceptives, untrained</td>
<td>80% group: increased NKCA, %CD56⁺ cells; 40% group: no differ. from control group</td>
<td>80% group: below control (90 min); 40% group: no change from control</td>
<td>40.5 ± 4</td>
<td>80% group: [norepinephrine] increased, returned to baseline (90 min)</td>
</tr>
<tr>
<td>Moyna et al. (1996)</td>
<td>Cycle ergometry at 55%, 70%, 85% VO₂max (6 min each)</td>
<td>32 M (24.6) 32 F (23.6) untrained</td>
<td>Incr. no. &amp; proportion of CD3⁻CD16⁺CD56⁺ cells; NKCA increase first 6 min, no change at 12, 18 min</td>
<td>Returned to baseline (2 hr)</td>
<td>37.8 ± 32.0</td>
<td>[Epinephrine] and [norepinephrine] increased at 12, 18 min, returned to baseline (2 hr)</td>
</tr>
<tr>
<td>Pedersen et al. (1990)</td>
<td>Cycle ergometry at 75% VO₂max (60 min)</td>
<td>15 M (20–29) untrained</td>
<td>NKCA and %CD16⁺ cells increased</td>
<td>NKCA below baseline (2 hr), returned to baseline (24 hr); %CD16⁺ cells returned to baseline (2 hr)</td>
<td>54.7</td>
<td>[Epinephrine] and [norepinephrine] increased, returned to baseline (2 hr)</td>
</tr>
<tr>
<td>Pedersen et al. (1988)</td>
<td>Cycle ergometry at 80% VO₂max (60 min); Back-muscle trng at 29% VO₂max (60 min)</td>
<td>6 M (23–28) untrained</td>
<td>Cycle: NKCA and proportion CD16⁺ cells increased; Back muscle: no change</td>
<td>Cycle: NKCA below baseline (2 hr), returned to baseline (24 hr); Back muscle: no change</td>
<td>–</td>
<td>Cycle: [epinephrine] and [norepinephrine] increased, returned to baseline (2 hr); [Cortisol] increased, below baseline (2 hr)</td>
</tr>
</tbody>
</table>

Note: NKCA = natural killer cell activity; [Epinephrine] = concentration of epinephrine; [Norepinephrine] = concentration of norepinephrine; [Cortisol] = concentration of cortisol; RM = repetition maximum.
Table 4  Possible Exercise-Induced Natural Killer Cell Activity Modulators in Elderly Persons

<table>
<thead>
<tr>
<th>Author</th>
<th>Exercise Type &amp; Duration</th>
<th>No., Gender, Age (yrs)</th>
<th>Effect on NKCA counts</th>
<th>Effects on Epinephrine, Norepinephrine, Cortisol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bermon et al. (2001)</td>
<td>8-week strength training intervention with acute strength test for immune measurements pre/posttraining</td>
<td>16 older adults (8 M, 8 F) (70.1)</td>
<td>Pretraining: elderly decreased NK cell count (~33%) after acute test; Posttraining: elderly slightly increased NK cell counts (+4.7%) after acute test; Young controls showed a 57.2% increase in [norepinephrine] after acute test</td>
<td>No increase pre/posttraining for elderly adults for epinephrine, norepinephrine, or cortisol; Young controls showed a 57.2% increase in [norepinephrine]</td>
</tr>
<tr>
<td>Flynn et al. (1999)</td>
<td>10-week resistance training intervention with acute resistance exercise for immune measurements pre/posttraining</td>
<td>15 F (72.6)</td>
<td>Prior to training, increase in CD3^+CD16^+CD56^+ immediately post-acute exercise, returned to baseline 2 hr post for exercise group; NKCA was higher for exercise group after acute exercise both pre- and posttraining; Training had no effect on NKCA overall</td>
<td>Training had no effects on serum cortisol levels overall.</td>
</tr>
</tbody>
</table>

Note: NKCA = natural killer cell activity; [Norepinephrine] = concentration of norepinephrine.
aging have included information about catecholamine or cortisol concentrations. Table 4 highlights two studies that have included these measurements. Neither the catecholamines (epinephrine and norepinephrine) nor cortisol appeared to modulate NKCA in the study by Bermon and associates (2001). Flynn and colleagues (1999) observed that training did not affect serum cortisol levels or NKCA in elderly women. With only two studies to date that have examined training effects on NKCA/NK cell counts, and catecholamines and/or cortisol, more research is warranted.

In Tables 2 and 3 we explore the possibility of catecholamine and cortisol modulation of exercise-induced changes in NK cell counts and NKCA in younger populations. Many acute-exercise studies have reported catecholamine and cortisol levels alongside NK cell counts and activity in younger subjects. For the most part, catecholamine levels were found to increase postexercise and return to baseline levels at 2 hours postexercise. This immediate postexercise increase is generally mirrored by an increase in NKCA and/or NK cell counts. However, NKCA generally falls below baseline values at 2 hours postexercise, returning to baseline after approximately 24 hours. Cortisol levels, on the other hand, do not behave in such a consistent manner from study to study.

It is generally accepted that plasma/serum cortisol levels increase during prolonged exercise or during exercise of high intensity (Galbo, 1981; Pedersen and Hoffman-Goetz, 2000). In the studies reviewed in Tables 2 and 3, cortisol levels generally increased postexercise, then promptly dropped below baseline levels at 2 hours postexercise. Therefore, exercise-induced cortisol levels could possibly be a modulator of NKCA. An exception was observed in a study by Mitchell and colleagues (2002) in which a decrease in cortisol levels occurred until 2 hours postexercise (Table 2). One confounding factor with studies on the effects of exercise on plasma cortisol concentration is the marked diurnal variation in cortisol secretion.

β-endorphin has also been studied as a possible modulator of NKCA during exercise. A recent review by Jonsdottir (2000a) reported that most studies have indicated that β-endorphin enhances NKCA. However, there is controversy as to the role of β-endorphin in modulating NKCA during exercise. Some authors suggest that β-endorphin is involved (Fiatarone et al., 1988) while others have failed to find any involvement (Gannon et al., 1998). Gannon and colleagues (1998) studied the effects of the ingestion of 50 mg of opioid antagonist naltrexone hydrochloride on NK cell counts and NKCA after 2 hours of moderate exercise. They found no difference in NK cell counts and NKCA, supporting the hypothesis that the increase in NKCA seen during exercise is not mediated by β-endorphin. Conversely, a similar study conducted by Fiatarone and associates (1988) concluded that the release of opioids during acute exercise seems to play a role in modulating NKCA during exercise.

**Clinical Relevance**

The ability of NK cells to destroy tumor cells has been reported often and is well accepted. However, they have limited ability to destroy massive tumors (Shephard and Shek, 1995). In addition, decreased immune function has been linked to an
increase in susceptibility to infections, degenerative diseases, morbidity, and mortality (Fahlman et al., 2000). It has been found that regular exercise training decreases incidences of self-reported upper respiratory tract infections (URTIs), and increases functional abilities through improved muscle function (Matthews et al., 2002). However, overtraining has been shown to increase susceptibility to URTIs. This relationship between URTI and exercise fits into the J-curve model, which suggests that although moderate exercise is associated with decreased URTI susceptibility, an excessive exercise workload is associated with increased susceptibility to URTI (Nieman, 1994). Another model, the “open window” theory, emphasizes the importance of measuring the degree of change in the immune response occurring immediately after a bout of prolonged exercise, a time of transient immunosuppression in which susceptibility to acute infections may increase (Hoffman-Goetz, 1998; Pedersen and Toft, 2000). The precise role of NK cells in these clinical trends is still uncertain, however.

There has been limited research on the relationship between exercise and URTIs in the elderly population. Most recently, Kostka et al. (2000) conducted both a retrospective and a prospective study of the incidence of URTIs in healthy elderly people. Participants were 33 men (age 71.3 ± 3.9 yrs) and 28 women (age 70.6 ± 3.7 yrs). For the retrospective component of the study, participants were asked to recall all URTIs suffered during the preceding year. A significant negative correlation was found between sports activity and the number of weeks with URTI per year. The 1-year prospective study reported a significant negative correlation between sports activity and both the number of URTIs per year and the number of days with URTI per year (Kostka et al., 2000).

Recently, Kmiec and colleagues (2001) reported that the NKCA of “optimally healthy” elderly was high (defined as >20% cytotoxicity) while the NKCA of “almost healthy” elderly was low (defined as <20% cytotoxicity). Optimal health was defined as fulfilling all SENIEUR protocol criteria. The SENIEUR protocol, developed by Ligthart and associates (1984), outlines exclusion criteria based on clinical information, laboratory data, and use of medications. Those who did not fulfill all criteria were designated “almost healthy” (Kmiec et al., 2001). Bruunsgaard and associates (2001) confirmed this finding. They found that a group of fragile elderly people, those with severe medical disorders known to influence immune function, had lower numbers of circulating NK cells in the blood compared to a healthy elderly group.

Combined with the knowledge that regular exercise training (both endurance and strength) has proven to be effective in reducing and preventing the loss of functional abilities that comes with aging, these results are strong incentives for elderly people to lead active lives (Mazzeo et al., 1998).

FUTURE DIRECTIONS

Of the immune function and exercise studies reviewed here, as with all human studies, there are limitations. Participants may be influenced by other factors which may ultimately confound results and conclusions. More and more, studies are beginning to account for factors such as diet, smoking status, substance abuse, underlying diseases, recent illness, activity levels, medication use, socioeconomic
status, and seasonal variations (Woods et al., 2002), all factors reported as influencing levels of NK cell activity. Additional complications are introduced by the effects of aging. Fiatarone and colleagues (1989) reported increased heterogeneity of responsiveness when comparing the effects of exercise on an older group of participants vs. a younger group. In addition, circadian variations have been reported, with maximum activity occurring in the morning or early afternoon (Whiteside et al., 1990). The development of a standard procedure for controlling the influences of these factors in this area of research would be helpful in comparing research results. Baseline NK cell activity can vary between individuals and reveal patterns of high and low responders. Ideally, future studies addressing the effects of exercise intervention will address this issue by randomly assigning individuals with different patterns of NK activity to the different treatment groups.

Criteria used for subject inclusion in studies is not standardized, and the degree of information given about subject health is varied; both factors can make direct comparisons of the degree of age-related change and the impact of exercise difficult. This point has been addressed by Kutza et al. (1995), who point out that inclusion criteria vary between studies, ranging from those adhering to the SENIEUR protocol to those using “apparently healthy” subjects. This observation further highlights the need for clear definition of the subjects’ health status, and of the criteria used to determine health status, especially in light of recent reports that factors such as nutritional status contribute to immune defects previously attributed entirely to senescence (Lesourd and Mazari, 1999).

Methods used in quantifying NK immune function have been varied. While most studies employ the Cr-release assay with K562 target cells (all studies reviewed here with one exception), different approaches are employed in presenting the results. In addition, some studies use whole blood while others use isolated PBMCs in the Cr-release assay. These differences make the comparison between studies difficult (Bryant et al., 1992; Kutza et al., 1995; Pross et al., 1981). Results may be presented as % cytotoxicity, % cytotoxicity per NK cell (lytic index), or as lytic units. NK cell concentrations, counts, and percentages (of lymphocytes and/or PBMC) have been determined using flow cytometry with different cell surface markers to identify NK cells.

While it is currently accepted that CD3–CD16+CD56+ identifies an NK cell, the recent discovery and characterization of natural killer cell receptors (NCR) may be a more accurate method of identifying NK cells (Moretta et al., 2001b; Rowbottom and Green, 2000). Finally, the quantification of NK activity is an in-vitro assay with a limited sample of peripheral blood that may or may not accurately reflect what is happening in vivo (Woods et al., 2002). Also, as outlined in the section on the biology of NK cells, there are several pathways used by NK cells to induce killing. The Cr-release assay measures only one of those pathways (Rowbottom and Green, 2000).

Both cross-sectional and longitudinal studies have been conducted on the effects of exercise or training on different parameters of immune function. There are strengths and weaknesses in both approaches (Mackinnon, 2000). For example, individual variability is a weakness in cross-sectional studies while competition, diet, season, and other stresses have been found to influence longitudinal studies (Mackinnon, 2000). In terms of the effects of training on NK cell activity and
numbers in the elderly population, more research is needed. There have been only four studies to date on the effects of resistance training on immune function in the elderly, with only three studying the effects on NK cells (Bermon et al., 2001; Flynn et al., 1999; Rincon et al., 1996). These four studies reported a slight increase or no change in NK cell function or counts with respect to resistance training. Nonetheless, more research should be conducted to confirm these results and to explore other approaches to enhancing NK cell activity, including nutritional interventions. Longer training interventions with larger sample sizes would give a broader perspective of the potential for exercise intervention to influence NK cells. Recent results suggest that long-term strength training in the elderly can improve NKCA (DiPenta et al., 2004). Longer interventions for endurance training are needed as well, if only to eliminate seasonal variations and other influencing factors.

CONCLUSION

The effects of training on natural killer cell numbers and activity in the elderly population are still unclear. Factors such as seasonal and lifestyle variations often skew the data. Long-term training eliminates these seasonal variations; however, no such studies have been conducted on the elderly. In addition, differences in methods of NKCA determination and presentation make it difficult to compare studies. This is an exciting new area of research in exercise immunology, notably with the advancing age of the Canadian population. We can expect many more studies addressing this topic in the future.

Acknowledgments

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Ligthart, G.J., Schuit, H.R., and Hijmans, W. (1989). Natural killer cell function is not diminished in the healthy aged and is proportional to the number of NK cells in the peripheral blood. *Immunology* 68: 396-402.


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