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Health- and Disease-Related Biomarkers in Aging Research

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Abstract

This article focuses on a synthesis of knowledge about healthy aging research in human beings and then synthesized nurse-led research in gerontology and geriatrics that use biomarkers. Healthy aging research has attracted considerable attention in the biomedical and basic sciences within the context of four major areas: (a) genetic variations as an expression of successful or unsuccessful aging; (b) caloric restriction as an intervention to slow the progression of aging; (c) immunological aging; (d) neurobiology of the aging brain. A systematic review of the literature was performed to identify nurse-led geriatric-related biomarker research. Nurse researchers who have chosen to integrate biomarkers as part of their research studies have been working in six focal areas, which are reviewed: health promotion within risk populations, cancer, vascular disease, Alzheimer's disease, caregiving, and complementary therapies. The article provides a discussion of contributions to date, identifying existing gaps and future research opportunities.

Focusing on biomarkers, rather than on health indicators, has been used to monitor both disease and deterioration in health status in older adults. However, this choice to focus on the paradigm of age-related decline neglects the potential to sustain or improve health status in older adults. More knowledge of health-related biomarkers is necessary to improve prevention and intervention methods that strengthen the healthy aspects of older adults as well as provide methods to monitor aspects of emerging or subclinical disease. This article first synthesizes pertinent knowledge about healthy aging research in human beings and then moves on to provide an integrative, critical review of nurse-led research in gerontology and geriatrics that uses biomarkers. The aim of this review is to discuss the contributions to date and identify existing gaps in this body of literature and recommendations for further development of this realm of science.

BACKGROUND

Aging is a complex process in single-cell eukaryotes, plants, fungi, animals, and human beings in which significant changes are observed in the genes, proteins, tissue structures, and physical abilities of older compared with younger forms of the species. Aging processes are the target of many biomarker discoveries intended to understand the multitude of physiological and pathophysiological processes of aging and are used to develop potential interventions to alter degeneration and disability in human beings and animals. A biomarker is defined by the National Institutes of Health (NIH) as “a characteristic that is objectively

measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention” (Biomarkers Definitions Working Group, 2001, p. 89). Two criteria commonly used to define a healthy aging phenotype is age at death or extreme longevity (>95 years) (Bladbjerg et al., 1999; Depp, Glatt, & Jeste, 2007; Ellsworth & Manolio, 1999; Glatt, Chayavichitsilp, Depp, Schork, & Jeste, 2007; Hadley & Rossi, 2005). This information is generally easy and reliable to obtain, yet is not necessarily a descriptor of healthy aging, but more a descriptor of life span, independent of health status.

Nurses are interested in promoting successful aging, which can be characterized by the positive attributes of maintaining high physical, cognitive, or social functioning, rather than the negative attributes of avoiding disease or disability (Manolio, 2007). Age to disease onset, disease-free survival, or level of functionality across multiple domains (e.g., physical, cognitive, social) might be better descriptors for healthy aging, or “healthspan” (Hadley & Rossi, 2005; Manolio, 2007).

THEORIES OF AGING

Several aging theories have been developed over the past 5 decades. These aging theories are divided into three major areas:

- The central “use it or lose it” dogma that assumes we use less of our mental and physical abilities as we age and therefore increasingly lose those abilities and functions over time (Corriveau, Hébert, Raïche, Dubois, & Prince, 2004; Mazzeo & Tanaka, 2001; van Petten, 2004).
- Gene mutations that cannot be repaired by the normal gene repair mechanisms and lead to irreversible changes in tissue function, cancer, accumulation of proteins, and other dysfunctions (Hamet & Tremblay, 2003; Loft, Fischer-Nielsen, Jeding, Vistisen, & Poulsen, 1993; Manolio, 2007).
- The mitochondrial dysfunction paradigm, which assumes that over time, mitochondrial DNA undergoes mutations that are not reversible, which leads to higher reactive oxygen species production, dysfunction in oxidative respiration, and changes in adenosine triphosphate uncoupling (Harman, 2006; Short et al., 2005).

These theories have guided the methodological developments of current basic and applied aging research.

HEALTHY AGING AND BIOMARKERS

Our literature search found that the healthy aging and biomarker literature contains 32 reviews, dating from 1990 to 2008. The attempt to find indicators in human beings that demonstrate critical steps in the healthy aging process has triggered the development of various aging cohort studies (de Groot, Verheijden, de Henauw, Schroll, & van Staveren, 2004; Garry, Wayne, & Vellas, 2007; Hochschild, 1990). Due to the mechanistic questions and invasive nature of the methods involved, the entire field has moved into the use of in vitro and in vivo model systems of flies, worms, and mice (Longo & Finch, 2003; Piper, Selman, McElwee, & Partridge, 2008). Since the early 1980s, healthy aging has attracted considerable attention in the biomedical and basic sciences within the context of four major areas:

- Genetic variations in age-related genes, chromosomal telomere length, and individual genes that expand or shorten the life span of a human being as an expression of successful or unsuccessful aging.

- Caloric restriction interventions to reverse aging processes and slow the progression of aging.
- Immunological aging to understand age-related changes in various immune cells.
- Neurobiological changes of the aging brain to explore cognitive and memory function as we age.

Genetic Factors in Healthy Aging

The completion of the Human Genome Project and the increasing knowledge of gene functions provide powerful opportunities to identify genetic variants associated with various diseases and disease traits (Manolio, 2007). Less research has been done to identify genes related to healthy aging, as most effort was put into disease-related studies. Currently, there is still a lack of a genetic phenotype of healthy aging, and most research in this area has been directed toward longevity (Cevenini et al., 2008; Tan, Zhao, Zhang, Kruse, & Christensen, 2008; Vijg & Campisi, 2008; Willcox et al., 2008); however, as noted above, longevity is not equivalent to successful or healthy aging.

Particularly valuable genotypes for genetic research include those with high heritability and close relationships to gene products and pathways, preferably with low, or at least measurable, environmental influences. One critical step in the discovery of genetic associations would be to define the appropriate phenotype of healthy aging. Healthy aging is a complex trait, most likely influenced by many genes with relatively small individual effects, different from a single gene disorder such as Huntington's disease (Gaspari et al., 2003; Greenwood, Sunderland, Friz, & Parasuraman, 2000; Rose et al., 2001). A genetic trait usually runs within a family, with the trait being more similar in families than among unrelated people. This familial resemblance can be found in a number of genetic studies of long-lived family members (Barja, 2008; Perls et al., 2000). Siblings of centenarians are four times more likely to survive into their ninth decade than siblings of individuals who have died before age 73. This provides some evidence that this trait may be influenced by genetics (Perls, Bubrick, Wagner, Vijg, & Kruglyak, 1998). Although this evidence is reflective of the study participants' longevity, it is not an indicator of their overall health status.

A candidate gene association and healthy aging is demonstrated in a study with the apolipoprotein E gene (*APOE*) (Seripa et al., 2006). *APOE* plays a critical role in lipoprotein metabolism and has been implicated as a risk factor in cardiovascular disease and dementia, and therefore could influence healthy aging. In a cross-sectional study of 1,344 healthy participants, the *APOE***E2* allele was found with a significantly higher frequency in men between ages 60 and 90 and in centenarians compared with those younger than 60, suggesting that the *APOE* genotype might be related to prolonged survival (Lunetta et al., 2007). However, this approach has limitations, as the biological association between the genes and the diseases might not be that obvious. For example, there is a complex relationship between the development of Alzheimer's disease and *APOE***E2* and *APOE***E4* genotypes, with the **E2* allele protective and the **E4* allele predictive of late-onset familial disease (Bird, 2008).

Recent advances in genotyping technology and generation of the human haplotype map have advanced genetic association studies of complex traits such as healthy aging. Instead of focusing solely on large family groups, genome-wide associations in complex traits of healthy aging phenotypes can now be assessed in unrelated individuals. A genome-wide association study involves genotyping individuals with and without the disease or trait for a high number of single nucleotide polymorphisms (SNPs), of which 10,000 to 1 million are located throughout the genome. SNPs with higher frequency among individuals with disease

than disease-free controls suggest an association with the SNP locus and the disease status. As part of the Framingham Study, five longevity and aging traits were identified for age at death in or near the following genes: forkhead box O1A (*FOXO1A*), glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*), klotho (*KL*), leptin receptor (*LEPR*), paraoxonase 1 (*PON1*), presenilin 1 (*PSE1*), mitochondrial superoxide dismutase 2 (*SOD2*), and Werner syndrome protein (*WRN*) (Lunetta et al., 2007). *FOXO1A* gene expression has also been implicated in life span extension in animal models, and *PON1* expression is associated with both age at death and morbidity-free survival at age 65 (Lunetta et al., 2007). These new opportunities to access large-scale and longitudinal data collection to perform genome-wide association studies should accelerate the identification of genetic associations with a healthy aging phenotype.

Caloric Restriction in Healthy Aging

More than 6 decades ago, reducing caloric intake was found to be the only conclusive and reproducible intervention to reverse aging and extend healthy life span in mammals (Yu, 1994). In a variety of animal models, dietary caloric restriction (CR) has been found to maintain physiological and behavioral functions and delays and reduce the severity of many age-related diseases (Roth, Ingram, & Lane, 2001; Weindruch & Waldorf, 1998). In 1984, the National Institute on Aging initiated the first large-scale controlled study of CR with primates. The researchers concluded that the intervention could indeed slow the signs of aging and maintain health and vitality (Lane, Ingram, & Roth, 1997). Combining the results of these and similar studies indicates that primates adherent to CR experience a slower age-related decline in circulating levels of the steroid hormone dehydroepiandrosterone sulfate (DHEAS); lower plasma concentrations of glucose, insulin, cholesterol, and triglycerides; lower systolic and diastolic blood pressure; less arterial stiffness; and increased insulin sensitivity and levels of high-density lipoprotein 2b (Ingram et al., 1990). Those primates were less likely to develop diabetes, cardiovascular disease, cancer, and other pathologies of aging than their fully fed counterparts. Unfortunately, human beings as a population are decidedly unlikely to ever adopt a CR lifestyle, even with the promise of an extended, healthy life span, due to side effects such as lowered body temperature and reduced activity levels and sexual desire. Difficulties with adherence and problems with the so-called “yo-yo” dieting are major examples of practical arguments against CR in human beings (Ingram et al., 1990). Recent promising results have been reported in mice using a class of novel therapeutic agents, sirtuins, which have CR-like properties without many of the negative side effects (Lavu, Boss, Elliott, & Lambert, 2008).

Immunological Biomarkers of Healthy Aging

The aging immune system is less efficient to cope with infectious diseases than the younger immune system, mainly because of altered immune responses to pathogens (Aw, Silva, & Palmer, 2007). Both the innate and the adaptive immune responses show age-related differences. Longitudinal studies in aging cohorts have allowed development of a definition of an “immune risk phenotype,” which predicts mortality in older adults on the basis of several parameters of the adaptive immune response. Although both innate and adaptive immunity undergo significant age-related changes, most studies have focused on the dramatic deterioration of the adaptive immune system with age. The percentage and the number of naïve T cells is lower in older adults because of age-associated thymic involution (Hince et al., 2008), while the percentage of memory T cells and effector memory cells is higher as a result of exposure to a wider variety of pathogens across the life span.

Maintaining a stable ratio between CD4 to CD8 T cells is an indicator of increased health and survival. In the absence of a stable T-cell ratio, increased rates of morbidity and mortality occur. The disappearance of naïve CD8 T cells increases in proportion to highly

differentiated CD8 T cells, which express no CD28, have short telomeres, and might be less functional, therefore suggesting that they have undergone a process of end-stage differentiation (Pfister et al., 2006). In older adults, these end-stage CD8 T cells often expand clonally in large numbers and are cytomegalovirus (CMV) specific (Weinberger et al., 2007). The majority of these cells are dysfunctional, with an impaired ability to secrete interferon gamma, suggesting that persistent CMV infection induces chronic stimulation of specific T cells. This leads to terminal differentiation into senescent cells with an altered functional capacity. Due to the lack of naïve T cells, this results in a self-perpetuating cycle, as in general, T cells must be activated by antigen presenting cells (APC) to initiate an appropriate immune response.

Dendritic cells (DCs), the main APCs of human beings, originate from progenitor cells in the bone marrow and differentiate in the peripheral tissue (Della Bella et al., 2007). During this process, they acquire the capacity to process, mature, and present antigens to CD8 and CD4 T cells with the help of major histocompatibility complex (MHC) class I and II molecules. After Toll-like receptors are activated on the DCs, they mature and migrate to secondary lymphoid tissue to present antigens to T cells and initiate the adaptive immunity (Comin et al., 2007). Mature DCs express high levels of MHC I and II, adhesion, and other co-stimulatory molecules, as well as chemokine receptors (DelaRosa et al., 2006). There is now a growing body of evidence that the DCs of frail older adults have a reduced ability to induce T-cell proliferation, decreased expression of co-stimulatory molecules, and lower interleukin 12 production (Uyemura, Castle, & Makinodan, 2002). In addition, the production of interleukin 10 is elevated in frail older adults, which suppresses DC maturation.

Natural killer (NK) cells are lymphocytes that recognize and kill virus-infected and tumor cells without the need for activation. They are critically important for the surveillance against CMV (Zhang et al., 2007). NK cells also regulate the immune response by producing cytokines and chemokines that participate in the elimination of pathogens and the activation of other immune cells. In healthy older adults, the NK cell cytotoxicity is not affected, which strengthens the notion that NK cell activity is critically important to healthy aging and longevity. Higher numbers of NK cells are related to better health status, lower mortality rates, and lower rates of upper respiratory infections among older adults. The described alterations in the adaptive and innate immunity point to distinct patterns as individuals age and could become part of the different phenotypes of healthy aging and frailty.

Normal Biology of the Aging Brain

As the brain ages, neuroanatomical, neurochemical, and physiological changes occur over time. Rather than being indicators of decline, these markers may also be related to functional reorganization and compensation, and instead be related to successful aging (Reuter-Lorenz & Lustig, 2005). Neuroanatomical changes with aging include the hallmark loss of brain volume (Mobbs, 2006; Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003) and a modest loss of synapses (Dekaban, 1978; Scheibel, Lindsay, Tomiyasu, & Scheibel, 1975), resulting in increased response time. However, there is also an expansion of the dendritic tree in response to the loss of synapses and reduction in the number of neurotransmitters (Dekaban, 1978; Timiras, 2003). This may explain the differences in functional magnetic resonance imaging (fMRI) studies between older adults and younger adults, which have demonstrated a pattern of overactivation linked to good performance, termed *compensation*, compared with younger counterparts (Reuter-Lorenz & Lustig, 2005). Thus, activation patterns seen in fMRI may be useful indicators of successful aging. Factors that may facilitate successful brain aging include longevity genes (as described above), exercise, cognitive training, and CR, while factors such as comorbid health conditions (e.g.,

hypertension, diabetes, depression) and social isolation may lead to functional decline (Meyer, Kawamura, & Terayama, 1994; Obrist, 1979; Reuter-Lorenz & Lustig, 2005).

SYNTHESIS OF NURSE-LED AGING RESEARCH USING BIOMARKERS

The literature was surveyed to identify which biomarkers have currently been integrated into nursing-led research focusing on older adults. A systematic review of the literature from 1989 to September 30, 2008 was undertaken using CINAHL Plus and PubMed. The databases were searched using the medical subject heading terms *biological markers*, *aged* or *aged 80 and over*, and *nursing research* and the following restrictions: *research articles* and *English*. The initial goal was to include only articles that restricted samples to adults age 65 and older; however, this was not possible as only four articles met this criteria, so the criteria were expanded to those that included older adults in the sample. In addition, we checked reference lists of selected studies to find additional studies. Abstracts were screened to discard studies that did not include older adults. From the expanded electronic database search, we identified 26 articles for analysis. Four articles (Bassett & Smyer, 2003; MacDonald, Sarna, Uman, Grant, & Weitzel, 2006; Oliffe, 2007; Setter, Corbett, Campbell, Cook, & Gates, 2003) used the biological marker conceptually and explored its use from an educational or practice perspective (e.g., the meaning of hemoglobin A1c to patients or providers), rather than its specific use as a variable of interest in the research analysis, thus they were excluded from this review. This left 22 articles for full review and analysis.

FINDINGS

Nurse researchers who have chosen to integrate biomarkers into their research studies have been working in six focal areas:

- Health promotion within at-risk populations.
- Cancer.
- Vascular disease.
- Alzheimer's disease.
- Caregiving.
- Complementary therapies.

The overwhelming majority of these biomarker research groups were collaborative in nature, with other disciplines such as medicine, pharmacy, microbiology, and immunology represented in the authorship lists (Gueldner et al., 1997; LaCroix et al., 2008). In addition, the publications represent the international nursing research community, including work from Japan (Deguchi, Deguchi, Wada, & Murashima, 2000; Sasajima et al., 2000), Taiwan (Huang, Lin, & Wang, 2008; Huang, Lin, & Yang, 2008; Yang, Chiang, Hsu, & Hung, 2008), China (Ren, Peng, Wu, Liao, & Sun, 2008), England (Galvin, Webb, & Hillier, 2001), Sweden (Bachrach-Lindstrom, Unosson, Ek, & Arnqvist, 2001), and the United States.

Biomarkers for Health Promotion Within At-Risk Populations

Health promotion and disease prevention research has been a hallmark of nursing science. In addition, the majority of the articles identified in this review were congruent with the current area of research emphasis of the National Institute of Nursing Research (2006b), which includes development of biomarkers that allows for the optimization of health through risk identification or moderation. Areas of emphasis include exercise, nutrition, smoking cessation, osteoporosis, and frailty.

Exercise—Nurse researchers have been interested in the biological effects of exercise on cohorts of healthy older adults (Gueldner et al., 1997) and those with osteoarthritis (Bautch, Clayton, Chu, & Johnson, 2000; Bautch, Malone, & Vailas, 1997). Exercise in older adults is known to have multiple benefits, including reduced risk of obesity and improved cardiovascular health. The effect of exercise on joint health in older adults is of particular interest in patients with osteoarthritis, which is highly prevalent (up to 85%) in older adults (Bautch et al., 1997). Walking's effect on the matrix of knee cartilage has been examined in two studies using synovial fluid biomarkers of cartilage degradation products: keratan sulfate, hydroxyproline, chondroitin sulphate, and sulfated glycosaminoglycan (Bautch et al., 1997, 2000). The 12-week exercise program was not associated with any significant changes in measured synovial biomarkers (Bautch et al., 1997, 2000), but older age was associated with lower levels of chondroitin sulphate and sulfated glycosaminoglycan, which may reflect the stage of the disease process (Bautch et al., 2000).

Individuals with reduced T-cell activity are at increased risk of morbidity and mortality. Because moderate exercise had been associated with improved immune function in some studies, but not in others, Gueldner et al. (1997) sought to explore the relationship between immune functioning (CD25 response) of women who participated in exercise classes for more than 15 years to those who were sedentary. Higher CD25 responses were found in the women who exercised, indicating better immune function. There are a number of ongoing exercise-focused research studies involving nurse researchers to promote improved function and reduce disability. However, as we found only three studies that incorporated biomarkers for this review, it is clearly an area of opportunity for nurse researchers to thoughtfully include biomarkers in their study designs.

Nutrition—Nutritional status is an important component in the health of older adults, and several markers of nutrition (body mass index [BMI], anthropometric data, and serum albumin) are common to the two studies identified in this review (Bachrach-Lindstrom et al., 2001; Yang et al., 2008). Other markers include total iron binding capacity (Yang et al., 2008), cortisol, insulin, insulin growth factor, and growth hormone levels (Bachrach-Lindstrom et al., 2001).

Bachrach-Lindstrom et al. (2001) enrolled a sample of women age 75 and older with hip fracture to either high-energy, high-protein meals or a standard diet and evaluated biomarkers at baseline and 3 months later. They found no significant differences in the groups on any of the chosen biomarkers. The two groups were matched for age, so no comparison could be made for aging effects in regard to nutritional biomarkers in this study. This is contrary to Yang et al. (2008), who found that older hemodialysis patients had poorer nutritional status, which is in line with findings from the general population (DiMaria-Ghalili & Amella, 2005). Therefore, studies of older adults using biomarkers should recognize the importance of increased age as a risk factor for declining nutritional status; thus the use of age matching may not be a useful design strategy.

Smoking Cessation—Studies of smoking behaviors often use self-report measures, which are often not reliable, and so researchers have turned to biomarkers of smoking behavior to objectively measure population risk (Huang, Lin, & Wang, 2008; Huang, Lin, & Yang, 2008) and response to smoking cessation interventions (Galvin et al., 2001). Expired carbon dioxide and salivary cotinine levels were found to be useful markers of smoking behavior, but gender differences were noted in the latter (Huang, Lin, & Yang, 2008). Urinary cotinine levels were evaluated by Galvin et al. (2001), but no significant differences were found, despite significant changes in carbon monoxide and behavioral indicators. The authors concluded that urinary cotinine levels are not recommended as a reliable biomarker of smoking status.

Osteoporosis—Bone loss in women after menopause is likely related to a combination of decreased bone formation and increased bone resorption, so most studies examining this problem have used biomarkers that reflect these processes. N-telopeptide of type I collagen (NTx), a marker of bone resorption; bone alkaline phosphatase, a marker of bone formation; and matrix metalloproteinase 1 (MMP-1), a membrane protein involved in both formation and resorption, have recently been evaluated for their association with risk for osteoporosis in middle-aged and older women (Lewis et al., 2000; Ren et al., 2008). NTx has been measured in both urine (Lewis et al., 2000) and serum (Ren et al., 2008) and is useful as a predictor of bone density and response to intervention. Bone alkaline phosphatase and MMP-1 levels are positively correlated with NTx (Ren et al., 2008) and reflect different aspects of bone turnover, and thus may be useful biomarkers for assessment of age-related bone changes. Depending on the kind of intervention, researchers may choose one or more of these biomarkers.

Another biomarker of bone loss is bone mineral density assessed via conventional dual-energy x-ray absorptiometry (DXA). DXA directs two different sources of photon energy toward the bone at a set frequency. These two sources of x-ray energy transmit bone density to be measured via a filter system; the greater the bone density, the stronger the signal. Gueldner et al. (2008) used an alternative system to measure heel bone mineral density by means of a novel alternative portable ultrasound technology to describe the incidence of osteoporosis in a sample of rural women. This choice allowed for improved community access to screening services and early diagnosis of bone loss and should be considered in future research designs. This method also has potential to become part of evidence-based practice for detection of bone loss in adults.

Frailty—Frailty in individuals has been associated with increased risk of morbidity and mortality (Fried, Ferrucci, Darer, Williamson, & Anderson, 2004; Phan, Alpert, & Fain, 2008; Varadhan, Seplaki, Xue, Bandeen-Roche, & Fried, 2008); therefore, interventions aimed at prevention of frailty or risk reduction in frail older adults are important for geriatric nurse researchers to pursue. At present, there is some discussion regarding the frailty phenotype, and several criteria have been proposed in the literature, including one by Woods et al. (2005) that involved an interdisciplinary team. Biomarkers that were indicative of frailty in this study included weight loss, grip strength, and kilocalories of energy expended in a week on leisure activities (Woods et al., 2005). These criteria were then used to evaluate the association between the pattern of statin medication use and the development of incident frailty in women age 65 and older (LaCroix et al., 2008). Statin drugs have anti-inflammatory properties and were hypothesized to be protective against development of frailty. However, no association between frailty and current statin medication use or duration was found, but a trend was reported for longer duration of statin drug use being protective (LaCroix et al., 2008).

To date, nurse researchers have not chosen to integrate markers of adaptive and innate immunity into studies of healthy aging and frailty, although other researchers have incorporated cytokines into their work (Varadhan et al., 2008). On the basis of our review of immune function in the healthy aging literature, a clear prospect exists for nurse researchers to incorporate immune biomarkers into research studies of frailty, with an opportunity to develop a solid conceptual basis.

Biomarkers in Studies of Prostate and Breast Cancer Patients

Cancer is a disease of aging, as increased age is a risk factor for most kinds of cancer. It is therefore not surprising that older adults would be included in studies conducted by nurse researchers in this population that have centered on solid tumors of the prostate (Conde et

al., 2004; Price, Hamilton, Robertson, Butts, & Freedland, 2008) and the breast (Payne, Held, Thorpe, & Shaw, 2008; Payne, Piper, Rabinowitz, & Zimmerman, 2006). BMI has been a biomarker of interest in studies of prostate cancer, as related to prostate-specific antigen (PSA) levels. Degree of obesity decreases PSA levels and necessitates alterations in treatment decision making (Price et al., 2008).

BMI is a risk factor for osteoporosis, where it may have implications for androgen deprivation therapy (Conde et al., 2004). Conde et al. (2004) measured bone densitometry (lumbar and femur) using DXA in two groups of men with prostate cancer and found that lower bone mineral density scores were associated with increased age, lower BMI, and higher PSA levels. Both of the prostate cancer studies were descriptive in nature, in contrast to the work by Payne et al. (2006, 2008), which examined the effects of exercise on symptoms of fatigue, mood, and sleep disturbances in breast cancer patients. Biomarkers of interest included serum measures (cortisol, serotonin, interleukin 6 [IL-6], melatonin, and bilirubin) and actigraphy (sleep). Although 12 weeks of exercise was not found by actigraphy to improve sleep efficiency in breast cancer patients ($n = 10$), there were significant differences in serum serotonin levels.

Previous work has demonstrated the beneficial effects of exercise in patients with depression (Babyak et al., 2000; Blumenthal et al., 2007), thus these preliminary findings are conceptually congruent and require further investigation. Of note, the circadian rhythm of certain biomarkers, such as melatonin and IL-6, make the timing of collection critical both within and across participants. Geriatric nurse researchers planning to integrate complex biomarkers relevant for cancer research into their designs need to be aware of the constraints that certain markers may place on sample collection and the additional burden this may place on older adults.

Using Multiple Biomarker Sources for Vascular Disease Risk Prediction

Nurse researchers have worked collaboratively to predict risk of disease and secondary conditions, such as delirium, in adult patients with or at risk for vascular disease. Depending on the focus of vascular disease, a number of different biomarkers have been used, including serum and plasma biomarkers (e.g., lipase, hemostatic markers, homocysteine levels), BMI, and vascular indexes (Badellino, Wolfe, Reilly, & Rader, 2008; Baldwin et al., 2007; Deguchi et al., 2000; Sasajima et al., 2000). Across all vascular populations studied by nurse researchers—peripheral vascular disease, cardiovascular disease (CD), and cerebrovascular disease—BMI was a critical biomarker for risk prediction. More than 30% of older adults in the United States are obese (Ogden, Carroll, McDowell, & Flegal, 2007); therefore, BMI is an important factor to be included in studies of risk and health promotion. Only one study integrated a technology-based biomarker into its study design. Ankle pressure measurement was predictive of postoperative delirium in participants with chronic lower limb ischemia (Sasajima et al., 2000). However, missing from these studies are validated vascular biomarkers, such as waist-to-hip ratio (WHR), coronary artery calcium scores, and carotid intima medial thickness. WHR was found to be significantly associated with the risk of incident cardiovascular disease events; a 1% increase in WHR is associated with a 5% increase in cardiovascular risk (de Koning, Merchant, Pogue, & Anand, 2007).

Coronary artery calcification, measured by chest computed axial tomography and a standardized scoring system, is associated with both prevalent coronary artery stenosis (Terry et al., 2005) and increased risk of cardiovascular events (Folsom et al., 2008). Carotid intima medial thickness is assessed by ultrasound technology. In the Multi-Ethnic Study of Atherosclerosis (Folsom et al., 2008), the hazard ratios for incident coronary heart disease were 2.5-fold higher per standard deviation increment in coronary artery calcium score and 1.2 fold higher for intima medial thickness.

Several of the studies attempted to use biomarkers to elucidate mechanistic pathways underlying differential risk profiles of groups at high risk for vascular disease. In a sample of 858 asymptomatic participants with a family history of premature CD, Badellino et al. (2008) found a positive correlation between plasma inflammatory markers and endothelial lipase, which lowers high-density lipoprotein cholesterol. This sample included 242 individuals with metabolic syndrome and did not include individuals older than 75, which is a limitation for interpretability to geriatrics.

Deguchi et al. (2000) studied a sample of older adults with and without risk factors for CD to determine whether plasma hemostatic biomarkers of plasmin activity and vascular endothelial damage (e.g., D-dimer levels) could be used to predict presence of disease. They reported that in individuals without disease, no alterations were found in any marker. However, in individuals with CD, elevations were found in D-dimer, soluble thrombin monomer, and plasmin- $\alpha 2$ inhibitory complex levels, which were more pronounced with increased age (>85).

Lastly, plasma homocysteine levels were used as a marker for stroke risk in a subsample of Mexican American ($n = 29$) and non-Hispanic White male veterans ($n = 29$), controlling for nutritional status (serum folate, B₁₂ levels) (Baldwin et al., 2007). Framingham Stroke Risk scores in Mexican American veterans were positively correlated to homocysteine levels; however, they were more likely to be out of the target range (10 to 15 $\mu\text{mol/L}$) than non-Hispanic White veterans and were not correlated to stroke risk in that group. These findings indicate that stroke risk profiles derived in one population may not translate well in another and could account for disparities in stroke risk detection.

Use of Genotype as a Biomarker for Alzheimer's Disease Risk

Alzheimer's disease (AD) is a common focus of research in the nursing literature, yet only one article was found that used biomarkers in this population (Schutte, Maas, & Buckwalter, 2003). The researchers compared the low-density lipoprotein receptor-related protein-associated protein 1 (*LRPAP1*) genotype with Alzheimer's disease phenotype in 37 participants. Using a candidate gene approach, the authors found a significant genotype effect of the *LRPAP1* insertion allele on activities of daily living, but not on cognition, specific AD behavior, or age of disease onset. In the discussion, they noted that positive findings in noncoding regions of the genome, such as this insertion polymorphism, would not be expected to directly alter gene expression.

The findings from this study are in contrast to prior work that found a protective effect of this allele for AD onset (Sánchez et al., 2001). Thus, there are difficulties in analysis and interpretation. Genetic studies such as the Schutte et al. (2003) study are frequently limited due to small samples and interpretability of the data. However, with the ongoing efforts to make genome-wide datasets publicly available (for a current list, see the Database of Genotypes and Phenotypes at <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gap>), nurse researchers who have the scientific expertise will be able to leverage these datasets to identify susceptibility genes for cohorts of at-risk individuals.

Biomarkers of Stress in Caregiving Research

Caregiving has been associated with both acute and chronic stress, which is known to alter the care provider's health status; thus, nursing research in this area has focused on identifying factors that could underlie these responses and affect caregivers' health-related quality of life. The conceptual framework underlying this is the psychoneuroimmunological (PNI) model, which states that the stress associated with caregiving induces immunosuppression via hypothalamic-pituitary-adrenal (HPA) axis activation (McCain,

Gray, Walter, & Robins, 2005). The hallmark biomarker of HPA axis activation in response to stress is cortisol elevation, with immunosuppressive effects occurring downstream of this activation. This immunosuppression would likely be increased in older caregivers due to the age-associated immune changes discussed above.

Three articles have been published that both focus on informal caregivers of adults with dementia and use biomarkers of caregiving stress (Davis et al., 2004; Garand et al., 2002; Lutgendorf et al., 1999). The groups measured different aspects of the response to caregiving. In an early study comparing various forms of stress and age effects on women, Lutgendorf et al. (1999) measured IL-6, a cytokine involved in the immune response and adrenocorticotrophic hormone secretion. They reported that IL-6 levels were higher in older caregivers than in all other groups, and that older women (caregivers, those anticipating a move out of the home, and a control group of noncaregiving, nonmoving older women) had higher levels of IL-6 compared with healthy, younger women.

Davis et al. (2004) used salivary cortisol production as a biomarker of activation to stress during caregiving situations ($n = 30$). Participants collected samples of their own saliva four times daily for 1 week at home; these measures were compared with self-reported diary entries regarding caregiving activities. They found cortisol production to be higher during caregiving events versus noncaregiving. No relationship was found between cortisol level and caregiver reports of depression. Similarly, Garand et al. (2002) found no change in mood as measured by the Profile of Mood States in caregivers ($n = 39$) following a community-based intervention; however, NK cell proliferation was significantly higher immediately following the intervention, but NK cell cytotoxicity activity was not different.

Stress reduction behavioral interventions are geared toward the psychological component of the PNI model. Therefore, they are intended to mediate stress reduction, and changes would occur via the impact on the HPA axis (McCain et al., 2005). In selecting a biomarker for the outcome variable in these behavioral studies, a more direct measure of mood change, such as cortisol, is a better correlate for efficacy than the more indirect NK cell activity. Immunological biomarkers could later be added to the design when effect sizes are determined for cortisol.

Biomarkers of Stress in the Intensive Care Unit During Integration of Complementary Therapies

Critical illness and injury are known to create increased stress on the body. This may result in physiological changes, such as in the sympathetic nervous system (SNS) and HPA axis, and ultimately metabolic changes, such as impaired oxygen transport and increased blood glucose levels, which worsen outcomes (Sommers & Bolton, 2006). Many interventions during critical illness are directed at managing the stress response or moderating its effects. Recently, the effect of music therapy on biomarkers of stress (SNS: epinephrine and norepinephrine; HPA axis: corticotrophin and cortisol) was evaluated in a small sample ($N = 10$) of adults ages 53 to 79 receiving mechanical ventilatory support in an intensive care unit (Chlan, Engeland, Anthony, & Guttormson, 2007). Serum biomarkers were collected at baseline and three times over the course of 60 minutes of music therapy ($n = 5$) and compared with those from a resting control group ($n = 5$). No significant changes were reported between the two groups on any marker in this pilot study. Due to critical illness, medications affecting the SNS were administered during the intervention period and may have influenced the results. Future studies using biomarkers of the SNS would need to control for this as a covariate.

DISCUSSION AND RECOMMENDATIONS

Nurse-led research using biomarkers has been primarily condition oriented, rather than focused on healthy aging processes, to derive evidence that supports management of the impact of disease on symptoms, function, and health-related quality of life. Many current biomarkers that nurse researchers integrate into studies with older adults are disease indicators of major organ systems but are not connected to their health status. The potential benefits of identifying biomarkers of healthy aging are to have bench-marks to maintain health status, to predict early changes, to follow the progression of changes, and to indicate stability, recovery, or both. One reason for the lack of focus on healthy aging is that nurse clinicians and geriatric nurse researchers may have fewer reasons to interact with healthy older adults, as they tend to live an independent lifestyle even if they choose to reside in a transitional living or retirement community. One question the gerontological and geriatric nurse researcher community needs to answer is: Are we interested in trying to set age-adjusted standard values for existing biomarkers, such as hormones of the HPA axis, or are we interested in discovering new biomarkers that could explain why certain older adults age with or without disease?

To date, there has been an omission to integrate the results of basic scientists working in healthy aging into the studies conducted by geriatric nurse researchers. For example, genes that have been identified in various animal models have yet to be tested in nurse-led studies. In addition, other important biomarkers have not been incorporated into nurse researchers' designs, such as WHR and coronary artery calcium scores. Extensive collaborations are needed to incorporate some of these biomarkers into nurse-led protocols. These efforts are actively supported and encouraged by the NIH Roadmap initiative and the National Institute of Nursing Research (2006a).

Nurse-led biomarker studies have focused on mechanistic pathways, basic biology, or epidemiology in humans beings and have added to the body of nursing knowledge through their concentration on risk reduction and prediction, disease prevention, reducing health disparities, and health-related quality of life. In the future, geriatric nurse researchers can continue to add to this body of knowledge in several ways. First, only four studies focused on adults age 65 and older. This speaks to the need for a more focused approach on older adults in future studies, including a cohort approach, which is common in biomedical studies. Second, most studies used cross-sectional designs. Given the influence of older age on the biomarkers reported in several of the studies and the inherent variability of biomarkers, the incorporation of longitudinal designs should be considered. The use of publicly available longitudinal datasets (e.g., Women's Health Initiative, Framingham Study) could be of great benefit to nurse researchers interested in this area. Finally, the large number of pilot studies with no subsequent follow-up publication is of concern. To conduct adequately powered studies and make meaningful inferences, additional resources need to be allocated to support nurse researchers working with biomarker discovery and use.

CONCLUSION

To better understand physiological and pathophysiological processes, identify potential therapeutic targets, and develop more sensitive outcome measures, biomarkers are being used increasingly in studies of aging. The use of these markers have many potential benefits for improving the health of older adults. Nurse researchers can maximally contribute to the body of knowledge in this area with thoughtful use of study designs, adequate sample sizes, and the use of multidisciplinary collaborations.

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