The Impact of the Nurses' Health Study on Population Health: Prevention, Translation, and Control

Graham A. Colditz, MD, DrPH, Sydney E. Philpott, BS, and Susan E. Hankinson, ScD

Objectives. To summarize the overall impact of the Nurses' Health Study (NHS) over the past 40 years on the health of populations through its contributions on prevention, translation, and control.

Methods. We performed a narrative review of the findings of the NHS, NHS II, and NHS3 between 1976 and 2016.

Results. The NHS has generated significant findings about the associations between (1) smoking and type 2 diabetes, cardiovascular diseases, colorectal and pancreatic cancer, psoriasis, multiple sclerosis, and eye diseases; (2) physical activity and cardiovascular diseases, breast cancer, psoriasis, and neurodegeneration; (3) obesity and cardiovascular diseases, numerous cancer sites, psoriasis, multiple sclerosis, kidney stones, and eye diseases; (4) oral contraceptives and cardiovascular disease, melanoma, and breast, colorectal, and ovarian cancer; (5) hormone therapy and cardiovascular diseases, breast and endometrial cancer, and neurodegeneration; (6) endogenous hormones and breast cancer; (7) dietary factors and type 2 diabetes, cardiovascular diseases, breast and pancreatic cancer, non-Hodgkin's lymphoma, neurodegeneration, multiple sclerosis, kidney stones, and eye diseases; and (8) sleep and shift work and chronic diseases.

Conclusions. The NHS findings have influenced public health policy and practice both locally and globally to improve women's health. (*Am J Public Health.* 2016;106:1540–1545. doi:10.2105/AJPH.2016.303343)

As noted in the individual articles in this series, the Nurses' Health Study (NHS) has evolved to address a broad range of lifestyle factors through questionnaires and biomarkers,[1] including diet, hormones, and trace elements. The study has also expanded from its initial funding to address breast cancer to include many other chronic conditions: type 2 diabetes, cardiovascular disease, fractures, rheumatological conditions, eye diseases, and other endpoints of interest in women's health. The NHS has informed an array of research areas including studies on obesity, kidney stones, skin conditions, less-common cancers, psychological factors (e.g., depression), and neurodegenerative diseases.

This expansion adds to the return on investment building the rich NHS cohort data through funding by the National Cancer Institute.[2] It also requires a continuity of funding to support the breadth and validity of health outcomes. To enable these efforts, the NHS has experimented with diverse innovations in infrastructure to maximize effectiveness and cost-efficiency, with many of these logistical innovations becoming common practice for other large epidemiological studies.[3] One of the most significant contributions is the use of optically scanned questionnaires and linkage to the National Death Index to complement active follow-up. However, among the most significant innovations introduced in NHS was the repeated assessment of habitual diet. The NHS has made key contributions in nutritional epidemiology research with the creation and validation of the Harvard Semiquantitative Food Frequency Questionnaire.[4] This improved efficiency has enabled the NHS to create an exceptional, large database of comprehensive, long-term, multidimensional information.

The use of data from prospective cohort studies such as the NHS has previously been addressed with regard to the overall impact of the National Cancer Institute–funded research program in cancer epidemiology.[5] That report focused primarily on the phases of the discovery, development, and delivery paradigm of cancer research. It also emphasized the importance of research findings from cohort studies and the need for their continued support. The existing National Cancer Institute–funded prospective cohorts, like the NHS, continue to provide key data that guide public health and clinical practice across many chronic conditions.[2] Evidence from cohort studies can help explain the etiology of disease with fewer sources of bias then other etiological designs. The broader contributions of cohorts in advancing our understandings of lifestyle and prevention of chronic conditions have been thoroughly summarized.[6,7]

This article summarizes some of the distinct contributions of the NHS and how the cohort has adapted to changing public health issues. We used the framework of discovery,

ABOUT THE AUTHORS

Graham A. Colditz and Sydney E. Philpott are with the Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine and Siteman Cancer Center, St Louis, MO. Susan E. Hankinson is with the Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA; the Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston; and the Department of Biostatistics and Epidemiology, School of Public Health and Health Sciences, University of Massachusetts, Amherst.

Correspondence should be sent to Graham A. Colditz, MD, DrPH, Washington University School of Medicine, Campus Box 8100, 600 S Taylor Ave, St Louis, MO 63110 (e-mail: colditzg@wudosis.wustl.edu). Reprints can be ordered at http://www.ajph.org by clicking the "Reprints" link.

This article was accepted June 20, 2016.

doi: 10.2105/AJPH.2016.303343

development, and delivery applied to epidemiology.[5] More extensive details are presented in the individual updates in this series.

DISCOVERY (DISEASE ETIOLOGY)

The purpose of epidemiological studies relating to discovery focuses on explaining the etiology of diseases and health conditions through hypothesis testing and identification of new risk factors.[5] The NHS is an example of a cohort that has sustained remarkable scientific productivity in the past 40 years, including more than 1200 publications that have substantially influenced prevention recommendations by many organizations, including the American Cancer Society, American Heart Association, Dietary Guidelines for Americans, and the World Health Organization.[3] The cohort follow-up has supported analysis of traditional risk factors through repeated measurements including change in weight[8,9] time since quitting smoking,[10] and change in diet, as well as contributed to the discovery and examination of additional risk factors associated with diet, physical activity, other lifestyle factors, biochemical pathways, and genetic data. In sum, such long follow-up allows the study and detailed analysis of the links between long-term or life-long exposures and diseases with very long lag times.

With regard to endogenous hormones, the NHS cohort, along with other cohorts, confirmed that circulating levels of estrogens and androgens were significantly associated with a higher risk of breast cancer before age 50 years,[11] and higher postmenopausal estrogen, androgen, and prolactin levels were related to estrogen receptor–positive breast cancer.[12]

Investigators have used the NHS to examine the role of specific biomarkers in disease risk. For example, the cohort identified novel biomarkers for incident type 2 diabetes, including adipokines, inflammatory cytokines, nutrition metabolites, and environmental pollutants.[13–17] Investigators also documented that higher levels of plasma carotenoids (present in fruits and vegetables, including alpha-carotene, beta-carotene, and lycopene) are inversely associated with breast cancer risk[18] and total folate intake 12 to 16 years before diagnosis is associated with reduced risk of colorectal cancer.[19,20]

The NHS cohort has also contributed to advances in genomic research and the investigation of genetics with regard to disease risk.[21] Genetic data have led to the identification of more than 90 common risk loci for breast cancer; the variants at these loci explain approximately 16% of familial risk of breast cancer.[22] For colorectal cancer patients with PIK3CA mutations, those who used aspirin regularly had improved cancer-specific survival and overall survival; however, among patients with wild-type PIK3CA, regular use of aspirin was not associated with cancer-specific or overall survival.[23] These genetic findings suggest that there should be greater importance placed on targeted interventions.

At a broader societal level, with NHS participants extending across the United States, opportunities have emerged for relating environmental exposures to health outcomes, particularly with regard to obesity[24] and type 2 diabetes.[16] Investigators have also assessed exposure in relation to built environment physical activity and body mass index (weight in kilograms divided by the square of height in meters).[25] Together, these examples demonstrate that individual biomarker level measures, behavior measures, and exposures at the group level (to built environment and air pollution) can all be integrated to refine our understanding of disease etiology.

DEVELOPMENT (THE BASIS FOR CONTROL MEASURES)

Epidemiological findings are a critical component of established approaches to the assessment of disease causality. These findings aim to provide a scientific basis for developing control measures and prevention strategies for groups and populations at risk and to develop needed public health measures and practices.[5] The NHS cohort has contributed to continued risk assessments and recognized additional exposure associations that help inform development of health recommendations.

The cohort has demonstrated the public health impact and potential for prevention by summarizing evidence on risk factors. Approximately 90% of type 2 diabetes cases may be prevented by diet and lifestyle modifications alone.[26] In addition, about 80% of CHD incidence could be prevented by avoidance of smoking, consuming a healthful diet, engaging in moderate to vigorous physical activity for at least 30 minutes most days, and consuming alcohol moderately (half to 1 drink per day).[27]

Studies also reported findings relating to cancer risks that are associated with lifestyle choices earlier in life. Breast cancer risk was confirmed to be associated with alcohol consumption in early and later adult life, even at low levels of consumption.[28] The risk of premenopausal breast cancer among women is higher when paired with greater consumption of red meat in high school[29] but risk is lower among women with higher intakes of fiber and fruit during adolescence.[30,31] The NHS has also identified novel lifestyle, dietary, environmental, serological, and genetic risk factors with regard to less-common cancers (endometrial, ovarian, pancreatic, and hematological). In addition, the cohort has helped clarify the importance of timing of exposure across the life course, such as earlier or later-in-life body size, to those risk associations and assessed heterogeneity or lack thereof, in etiological associations across discrete tumor subtypes.[32]

The expanding scope of the cohort has allowed investigators to explore the relations between lifestyle and neurodegeneration and associated diseases. Results demonstrated that greater intake of antioxidants,[33] higher nut intake,[34] and following the Mediterranean diet[35] are all associated with higher cognitive functioning.

The NHS has contributed to continued risk factor assessments over extended periods of time. Repeated assessments of exposures over time have included weight, smoking, and dietary patterns. For example, the NHS cohort has confirmed that excess adiposity is the strongest risk factor for type 2 diabetes,[36] and weight across the life course and obesity are strongly but variably associated with risk of cardiovascular disease,[9,37] breast cancer,[8] endometrial cancer,[38,39] and pancreatic cancer.[40]

Risk prediction models also integrate risk factors to guide stratification and prioritizing of risk-reduction strategies. The NHS data are the basis for models of cardiovascular disease,[41] melanoma, and cancer of the breast,[42] ovary, and colorectum.[43]

In the box on the next page, we list many of the significant findings from the NHS that pertain to the association of lifestyle, behavioral, and dietary risk factors, and environment with risk of specific diseases.

IMPORTANT OUTCOMES FROM THE NURSES' HEALTH STUDY AND ASSOCIATED SIGNIFICANT FINDINGS

Outcome	Significant Findings
Related to smoking	
Type 2 diabetes	Passive and active smoking is associated with increased type 2 diabetes risk.
Cardiovascular disease	Smoking is associated with CVD in women.
Colorectal cancer	Cigarette smoking is associated with increased risk of colorectal adenoma and colorectal cancer.
Pancreatic cancer	Cigarette smoking is an important pancreatic cancer risk factor.
Psoriasis	Smoking is significantly associated with increased psoriasis risk.
Multiple sclerosis	Current cigarette smokers have increased risk of MS compared with never smokers.
Eye diseases	Smoking is associated with increased risk of cataracts and age-related macular degeneration.
Related to physical activity	
Type 2 diabetes	Sedentary behavior increased type 2 diabetes risk and moderate- to high-intensity exercise lowered type 2 diabetes risk.
Cardiovascular disease	Moderate-intensity physical activity is associated with lower risk of CHD.
Breast cancer	Participating in ≥7 h moderate to vigorous physical activity per week decreases risk of breast cancer.
Psoriasis	Lack of physical activity is a major risk factor for psoriasis.
Neurodegeneration	Higher levels of physical activity are associated with better cognitive performance.
Associated with obesity	
Type 2 diabetes	Excess adiposity is the strongest type 2 diabetes risk factor.
Cardiovascular disease	Even moderate weight gain since age 18 y is associated with subsequent risk of CHD incidence and CVD mortality.
Breast cancer	Short-term weight gain is associated with increased breast cancer risk that was strongest for premenopausal women.
Endometrial cancer	Obesity accounts for approximately 40% of incident endometrial cancer cases.
Pancreatic cancer	Overweight or inactive women have positive associations with pancreatic cancer risk.
Non-Hodgkin's lymphoma	Adiposity in young adulthood, adolescence, and childhood is strongly associated with non-Hodgkin's lymphoma risk.
Psoriasis	Overall and central obesity is associated with increased risk of psoriasis.
Multiple sclerosis	Individuals who are obese have greater risk of MS.
Kidney stones	Obesity and weight gain are both associated with higher risk of kidney stone formation.
Eye diseases	Obesity and high BMI are associated with cataracts.
Related to oral contraceptives	
Cardiovascular disease	Current OC use is associated with higher risk of CVD, primarily among women who are smokers and those with hypertension.
Cancer	Mixed effects among current OC users suggesting a higher risk of melanoma and breast cancer, and a lower risk of colorectal and ovarian cancer.
Related to postmenopausal hormone therapy	
Cardiovascular disease	Current HT use is generally associated with lower risk of total CHD and nonfatal myocardial infarction.
Breast cancer	Current combined used of estrogen and progestin is associated with increased risk of breast cancer.
Endometrial cancer	Postmenopausal estrogen use is one of the best-established risk factors for endometrial cancer.
Neurodegeneration	Past or current HT users have significantly worse rates of decline in global cognition.
Related to endogenous hormones	
Breast cancer	Circulating levels of estrogens and androgens are significantly positively associated with risk of breast cancer.
Related to dietary factors	
Type 2 diabetes	Dietary patterns that increase intake of fruits, vegetables, whole grains, and legumes, while decreasing intake of red meats, refined sugars, and sugar-sweetened beverages decrease risk of type-2 diabetes.
Cardiovascular disease	Diet is an important determinant of CVD risk, and trans-fatty acids are strongly associated with CHD risk.
Breast cancer	Dietary pattern characterized by higher intake of fruits, vegetables, whole grains, low-fat dairy, fish, and poultry decreased risk of breast cancer.
Pancreatic cancer	There are positive associations between pancreatic cancer risk and intake of fructose and sugar-sweetened soft drinks and an inverse association between vitamin D and pancreatic cancer risk.
Non-Hodgkin's lymphoma	There is a significant increased risk of non-Hodgkin's lymphoma associated with intake of trans fat and red meat.
Neurodegeneration	Greater intake of antioxidants, higher nut intake, and following the Mediterranean diet all are associated with higher cognitive functioning.

Continued

Continued

Outcome	Significant Findings
Multiple sclerosis	Vitamin D intake may be associated with reduced MS risk.
Kidney stones	DASH diet (high in fruits and vegetables, moderate in low-fat dairy products, and low in red and processed meats) contributes to kidney stone prevention.
Eye diseases	Maintaining a healthy and well-balanced diet helps prevent cataracts, age-related macular degeneration, and primary open-angle glaucoma.
Related to environment	
Obesity	Higher levels of bisphenol A and phthalates (byproducts of plastics and other consumer goods) are associated with weight gain. Those living in higher-density counties (i.e., lower sprawl) had lower BMI and higher physical activity.
Type 2 diabetes	Higher urinary levels of persistent organic pollutants and bisphenol A and phthalates are significantly associated with higher type 2 diabetes risk.
Squamous cell carcinoma	Exposure to the sun leading to sunburn, particularly at early ages, increases the risk of incident squamous cell carcinoma.
Related to sleep and shift work	
Type 2 diabetes	Too long and too short duration of sleep and decreased quality of sleep increase risk of type 2 diabetes.
Cardiovascular disease	Shift work and not sleeping the optimal 8 h a day is associated with increased risk of CHD.
Breast cancer	There is a positive association between number of years working night shifts and risk of breast cancer.
Colorectal cancer	Higher consumption of animal fat (and processed meats) is associated with higher colon cancer risk, whereas increased consumption of fiber, folate, and vitamin D decrease colon cancer risk.

Note. BMI = body mass index (kg/m^2); CHD = coronary heart disease; CVD = cardiovascular disease; DASH = dietary approaches to stop hypertension; HT = hormone therapy; MS = multiple sclerosis; OC = oral contraceptives.

DELIVERY (IMPLEMENTATION OF FINDINGS)

The impact of the NHS extends to the implementation of findings by the public, clinicians, health practitioners, policymakers, industry, and others. Specifically, the cohort has allowed an expanded scope of study that continues to inform policy and practice.

Many findings from the NHS have contributed to public health recommendations summarized in World Health Organization, World Cancer Research Fund, and various reports from the US Surgeon General.[44] For example, the Food and Drug Administration acted, in part, on evidence from the NHS relating dietary trans-fat consumption to both heart disease and diabetes risk. Removal of trans-fat in Canada and the United States has resulted in decreased incidence of heart disease and diabetes.[45,46] Estimates suggest that this population benefit is a decrease by more than 12% in the number of incident cases of diabetes and a more than 8% decrease in CVD.

Nurses' HealthStudy research on the benefits of physical activity on disease prevention and premature mortality contributed to the evidence base for the 2008 Physical Activity Guidelines for Americans.[47] Research over more than 20 years on use of postmenopausal hormone therapy was also key in shifting the discussion about hormone therapy safety and appropriateness of use. The data published in 1995 showed that breast cancer risk increased with increasing duration of hormone therapy use, particularly for combination estrogen-plus-progestin. With this finding (later confirmed by the Women's Health Initiative randomized trial), the focus of hormone therapy use moved from the long-held stance that "ever use" was safe, to a more appropriate discussion about "duration of use" and the risks and benefits of hormone therapy.

Studies of survivorship after cancer diagnosis and treatment have been broadened to address physical activity and diet changes, showing that higher levels of physical activity reduce risk of recurrence and death among women with breast and colon cancer,[48] and contribute to guidelines for cancer survivors.[49]

EXPANDING SCOPE OF STUDY

The NHS continues to evolve and explore new areas of etiological and translational research. The cohort is expanding to assess innovations in use of mobile technology as well as working to link information regarding NHS participants' health and health care utilization.[3] Repeated blood collections allow for analysis of change in markers and change in risk to parallel studies of change in adherence to diet guidelines and risk of disease. In addition, with collection of repeated exposure data both before and after cancer diagnosis, the cohort can evaluate when components of lifestyle are important to survival during the disease process, and offer key findings with tangible clinical implications. The availability of data on health and health-related quality of life before and after cancer diagnosis allows for valuable insights into the causes and consequences of cancer on health and well-being.

Recently, the NHS has applied metabolomics to the biology of cancer, potentially uncovering novel pathways in etiology and survival, as well as new targets for intervention.[50] These metabolomic measures are being expanded to assess health implications in the cohort with regard to hypertension, chronic obstructive pulmonary disease and asthma, and fertility, as well as more detailed data on the impact of alcohol use and disease outcomes.

In addition to further analyzing these aspects of health, the NHS is expanding participant recruitment. Since 1976 when the NHS began, the demographics of nursing have greatly changed with increasing proportions of minorities and men joining the profession. As such, recruitment extended in 2012 to prioritize enrollment of minority

participants and in January 2015 the NHS3 began recruiting men as primary study participants.[3]

CONCLUSIONS

Collectively, the NHS has contributed substantially to the understanding of numerous health- and disease-related outcomes in women. Many of these contributions have been made possible through external collaborations with researchers across the globe including a number of pooling projects that combine individual participant data to reduce heterogeneity in approaches to analysis and also allow for the study of rarer endpoints that are not frequent enough for individual cohorts to publish robust findings.[51] These pooled analyses reduce publication bias for these endpoints. This collaborative expansion continues to evolve and inform guidelines and future research projects.

The NHS has helped refine methods for conduct of prospective cohort studies including measures of exposures, data analysis, statistical methods, and approaches to linking of data sources to inform urban design, air pollution guidelines, and other exposure measures that are now more readily available to investigators. The scope of health conditions being investigated and documented in the cohort all add to the sustained value of the NHS as summarized in this supplement. This study serves as a model prospective cohort study with repeated measurement that is having an impact on public health policy and practice both locally and globally. AJPH

CONTRIBUTORS

All authors outlined the article and S. E. Philpott wrote the first draft. G. A. Colditz and S. E. Hankinson provided extensive revisions of the text. All authors conceptualized and designed the report, revised all iterations, and approved the final version for submission.

ACKNOWLEDGMENTS

This work was funded by the following National Institutes of Health grants: R01 CA050385, UM1 CA186107, P01 CA087969, UM1 CA176726, and R01 CA67262. S. E. Philpott and G. A. Colditz were also supported by the Foundation for Barnes-Jewish Hospital.

The authors would also like to thank the participants and staff of the Nurses' Health Study and Nurses' Health Study II for their valuable contributions as well as the following state cancer registries for their help: Alaska, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, Florida, Georgia, Idaho, Illinois, Indiana, Iowa, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Nebraska, New Hampshire, New Jersey, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, Virginia, Washington, and Wyoming.

Note. The authors assume full responsibility for analyses and interpretation of these data.

HUMAN PARTICIPANT PROTECTION

The Nurses' Health Study protocols have been approved by the Brigham and Women's Hospital institutional review board and accepted by Harvard T. H. Chan School of Public Health.

REFERENCES

1. Colditz GA, Hankinson SE. The Nurses' Health Study: lifestyle and health among women. *Nat Rev Cancer*. 2005; 5(5):388–396.

2. Colditz GA. Cohort studies of etiology and survival after cancer: the unique needs for uninterrupted funding. *Cancer Causes Control*. 2007;18(3):235–241.

3. Bao Y, Bertoia ML, Lenart EB, et al. Origin, methods, and evolution of the 3 Nurses' Health Studies. *Am J Public Health*. 2016;106(9):1573–1581.

4. Salvini S, Hunter DJ, Sampson L, et al. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. *Int J Epidemiol*. 1989;18(4):858–867.

5. Colditz GA, Winn DM. Criteria for the evaluation of large cohort studies: an application to the Nurses' Health Study. *J Natl Cancer Inst*. 2008;100(13):918–925.

6. Willett W. Diet and coronary heart disease. In: *Nutritional Epidemiology*. Oxford, UK: Oxford Scholarship Online; 1998: 341–379.

7. Willett WC, Dietz WH, Colditz GA. Guidelines for healthy weight. *N Engl J Med*. 1999;341(6):427–434.

8. Rosner B, Eliassen AH, Toriola AT, et al. Short-term weight gain and breast cancer risk by hormone receptor classification among pre-and postmenopausal women. *Breast Cancer Res Treat*. 2015;150(3):643–653.

9. Willett WC, Manson JE, Stampfer MJ, et al. Weight, weight change, and coronary heart disease in women: risk within the "normal" weight range. *JAMA*. 1995;273(6): 461–465.

10. Kenfield SA, Stampfer MJ, Rosner BA, Colditz GA. Smoking and smoking cessation in relation to mortality in women. *JAMA*. 2008;299(17):2037–2047.

11. Key TJ, Appleby PN, Reeves GK, et al.; the Endogenous Hormones and Breast Cancer Collaborative Group. Sex hormones and risk of breast cancer in premenopausal women: a collaborative reanalysis of individual participant data from seven prospective studies. *Lancet Oncol*. 2013;14(10):1009–1019.

12. Tworoger SS, Eliassen AH, Zhang X, et al. A 20-year prospective study of plasma prolactin as a risk marker of breast cancer development. *Cancer Res*. 2013;73(15): 4810–4819.

13. Hu FB, Meigs JB, Li TY, Rifai N, Manson JE. Inflammatory markers and risk of developing type 2 diabetes in women. *Diabetes*. 2004;53(3):693–700.

14. Meigs JB, Hu FB, Rifai N, Manson JE. Biomarkers of endothelial dysfunction and risk of type 2 diabetes mellitus. *JAMA*. 2004;291(16):1978–1986.

15. Rajpathak SN, He M, Sun Q, et al. Insulin-like growth factor axis and risk of type 2 diabetes in women. *Diabetes*. 2012;61(9):2248–2254.

16. Sun Q, Wedick NM, Tworoger SS, et al. Urinary excretion of select dietary polyphenol metabolites is associated with a lower risk of type 2 diabetes in proximate but not remote follow-up in a prospective investigation in 2 cohorts of US women. *J Nutr*. 2015;145(6):1280–1288.

17. Ding M, Franke AA, Rosner BA, et al. Urinary isoflavonoids and risk of type 2 diabetes: a prospective investigation in US women. *Br J Nutr*. 2015;114(10): 1694–1701.

18. Eliassen AH, Liao X, Rosner B, Tamimi RM, Tworoger SS, Hankinson SE. Plasma carotenoids and risk of breast cancer over 20 y of follow-up. *Am J Clin Nutr*. 2015;101(6):1197–1205.

19. Giovannucci E, Stampfer MJ, Colditz GA, et al. Folate, methionine, and alcohol intake and risk of colorectal adenoma. *J Natl Cancer Inst*. 1993;85(11): 875–884.

20. Cho E, Zhang X, Townsend MK, et al. Unmetabolized folic acid in prediagnostic plasma and the risk of colorectal cancer. *J Natl Cancer Inst*. 2015;107(12): djv260.

21. Hunter DJ, Riboli E, Haiman CA, et al. A candidate gene approach to searching for low-penetrance breast and prostate cancer genes. *Nat Rev Cancer*. 2005;5(12): 977–985.

22. Michailidou K, Beesley J, Lindstrom S, et al. Genome-wide association analysis of more than 120,000 individuals identifies 15 new susceptibility loci for breast cancer. *Nat Genet*. 2015;47(4):373–380.

23. Liao X, Lochhead P, Nishihara R, et al. Aspirin use, tumor PIK3CA mutation, and colorectal-cancer survival. *N Engl J Med*. 2012;367(17):1596–1606.

24. Song Y, Hauser R, Hu F, Franke A, Liu S, Sun Q. Urinary concentrations of bisphenol A and phthalate metabolites and weight change: a prospective investigation in US women. *Int J Obes (Lond)*. 2014;38(12):1532–1537.

25. James P, Troped PJ, Hart JE, et al. Urban sprawl, physical activity, and body mass index: Nurses' Health Study and Nurses' Health Study II. *Am J Public Health*. 2013;103(2):369–375.

26. Hu FB, Manson JE, Stampfer MJ, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med*. 2001;345(11):790–797.

27. Stampfer MJ, Hu FB, Manson JE, Rimm EB, Willett WC. Primary prevention of coronary heart disease in women through diet and lifestyle. *N Engl J Med*. 2000; 343:16–22.

28. Liu Y, Colditz GA, Rosner B, et al. Alcohol intake between menarche and first pregnancy: a prospective study of breast cancer risk. *J Natl Cancer Inst*. 2013;105(20):1571–1578.

29. Farvid MS, Cho E, Chen WY, Eliassen AH, Willett WC. Adolescent meat intake and breast cancer risk. *Int J Cancer*. 2015;136(8):1909–1920.

30. Farvid MS, Eliassen AH, Cho E, Liao X, Chen WY, Willett WC. Dietary fiber intake in young adults and breast cancer risk. *Pediatrics*. 2016;137(3):1–11.

31. Farvid M, Chen W, Michels K, Cho E, Willett WC, Eliassen AH. Fruit and vegetable consumption in adolescence and early adulthood and risk of breast cancer: population based cohort study. *BMJ*. 2016;353:i2343.

32. Tamimi RM, Colditz GA, Hazra A, et al. Traditional breast cancer risk factors in relation to molecular subtypes of breast cancer. *Breast Cancer Res Treat*. 2012;131(1):159–167.

33. Devore EE, Kang JH, Breteler M, Grodstein F. Dietary intakes of berries and flavonoids in relation to cognitive decline. *Ann Neurol*. 2012;72(1):135–143.

34. O'Brien J, Okereke O, Devore E, Rosner B, Breteler M, Grodstein F. Long-term intake of nuts in relation to

cognitive function in older women. *J Nutr Health Aging*. 2014;18(5):496–502.

35. Samieri C, Okereke OI, Devore EE, Grodstein F. Long-term adherence to the Mediterranean diet is associated with overall cognitive status, but not cognitive decline, in women. *J Nutr*. 2013;143(4):493–499.

36. Hu FB. Metabolic consequences of obesity. In: *Obesity Epidemiology*. New York, NY: Oxford University Press; 2008: 149–173.

37. Yakoob MY, Shi P, Hu FB, et al. Circulating biomarkers of dairy fat and risk of incident stroke in US men and women in 2 large prospective cohorts. *Am J Clin Nutr*. 2014;100(6):1437–1447.

38. Kaaks R, Lukanova A, Kurzer MS. Obesity, endogenous hormones, and endometrial cancer risk: a synthetic review. *Cancer Epidemiol Biomarkers Prev*. 2002; 11(12):1531–1543.

39. Bergström A, Pisani P, Tenet V, Wolk A, Adami HO. Overweight as an avoidable cause of cancer in Europe. *Int J Cancer*. 2001;91(3):421–430.

40. Michaud DS, Liu S, Giovannucci E, Willett WC, Colditz GA, Fuchs CS. Dietary sugar, glycemic load, and pancreatic cancer risk in a prospective study. *J Natl Cancer Inst*. 2002;94(17):1293–1300.

41. Chiuve SE, Cook NR, Shay CM, et al. Lifestyle-based prediction model for the prevention of CVD: the Healthy Heart Score. *J Am Heart Assoc*. 2014;3(6):e000954.

42. Rosner BA, Colditz GA, Hankinson SE, Sullivan-Halley J, Lacey JV II, Bernstein L. Validation of Rosner-Colditz breast cancer incidence model using an independent data set, the California Teachers Study. *Breast Cancer Res Treat*. 2013;142(1):187–202.

43. Wei EK, Colditz GA, Giovannucci EL, Fuchs CS, Rosner BA. Cumulative risk of colon cancer up to age 70 years by risk factor status using data from the Nurses' Health Study. *Am J Epidemiol*. 2009;170(7):863–872.

44. *The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General*. Atlanta, GA: National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014.

45. *Dietary Guidelines for Americans*. Washington, DC: Department of Agriculture, Department of Health and Human Services; 2010.

46. *Scientific Report of the 2015 Dietary Guidelines Advisory Committee*. Washington, DC: US Department of Agriculture and US Department of Health and Human Services; 2015.

47. *Physical Activity Guidelines Advisory Committee Report, 2008*. Washington, DC: Physical Activity Guidelines Advisory Committee, US Department of Health and Human Services; 2008.

48. Holmes MD, Chen WY, Feskanich D, Kroenke CH, Colditz GA. Physical activity and survival after breast cancer diagnosis. *JAMA*. 2005;293(20):2479–2486.

49. Rock CL, Doyle C, Demark-Wahnefried W, et al. Nutrition and physical activity guidelines for cancer survivors. *CA Cancer J Clin*. 2012;62(4):243–274.

50. Townsend MK, Clish CB, Kraft P, et al. Reproducibility of metabolomic profiles among men and women in 2 large cohort studies. *Clin Chem*. 2013;59(11): 1657–1667.

51. Teras LR, Kitahara CM, Birmann BM, et al. Body size and multiple myeloma mortality: a pooled analysis of 20 prospective studies. *Br J Haematol*. 2014;166(5): 667–676.

EDITOR'S NOTE

Because of space restrictions and the large volume of references relevant to the Nurses' Health Study, additional references are provided in a supplement to the online version of this article at http://www.ajph.org.