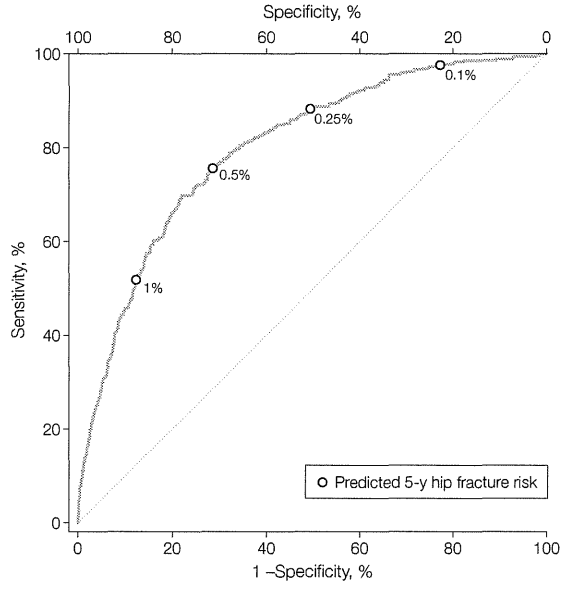
more women at risk of hip fracture, approximately 75% of women who would have hip fractures in the next 5 years, but one would double the rate of overdiagnosis. There would be a false-positive rate of 30%. Seventy-five percent of the hip fractures in the next 5 years would occur in this group, but 30% of the women predicted to have hip fractures would not.

As a final step, we compared the predictive value of the algorithm with the DXA measurements of the women whose BMD was measured. There were 10 750 women with DXA measurements who either completed at least 5 years of follow-up or experienced a hip fracture. The combined group had 80 hip fractures over a mean (SD) of 8.7 (1.2) years of follow-up; thus, the power to show a difference was small. ROC curves were calculated for the algorithm, the DXA, or a combination of the 2. These are shown in FIGURE 3. There was no statistically significant difference in the AUCs.

To show the relative utility of the models prediction based on the 5% highest-risk group for the DXA (T score ≤−2.5) and the 5% highest-risk group for the point-scoring method (score ≥21 points) were compared (A T score is a standard deviation of the bone density above the peak average for a young woman); 3.8% of the high-risk DXA group went on to have hip fractures in 5 years compared with 3.1% of the high-risk point-score group (TABLE 4).

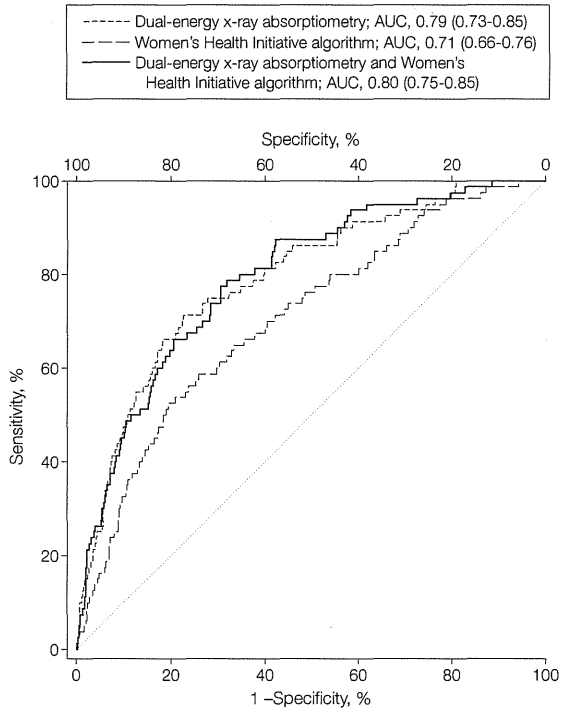
Noting that the number of women with a hip fracture in the subset with DXA scans was small, we compared the women identified by DXA and the point-scoring algorithm using the same cut points The results are shown in TABLE 5, which demonstrates the discordance between the 2 methods of prediction and actual outcomes. We also note that the women who were identified by only 1 method of prediction have had a substantial increased risk of fracture compared with the women who were not identified by either method.

Figure 2. Sensitivity and 1-Specificity of Receiver Operating Characteristic at Selected Percentage Predictions of 5-Year Risk of Hip Fracture



AUC indicates area under the curve. Blue curves in Figure 1 and Figure 2 are the same and are derived from the entire clinical trial cohort.

Figure 3. Comparison of the Women's Health Initiative Algorithm With Results From Dual-Energy X-ray Absorptiometry Scans



AUC indicates area under the curve. Data are based on a subset of 10 750 women with bone mass density measurements.

TABLE 6 shows the median 5-year hip fracture risk and the 2.5% upper and lower limits for this prediction, according to a simple sum point score that approximates the WHI probability score. This can also be done using the online algorithm.

Table 4. Comparison of the Prediction of 5-Year Risk of Hip Fracture in the 5% Highest Risk Group by Point Score and DXA

	Patients With Hip Fractures		Patients Without Hip Fractures	
	Observed	Predicted	Observed	Predicted
DXA				
>T score −2.5	60	57.0	10 165	10 169
<T score −2.5	20	23.0	504	501
WHI				
<21 points	65	64.9	10 203	10 203.1
≥21 Points	15	15.1	467	466.9

Abbreviations: DXA, dual-energy x-ray absorptiometry; T score, a standard deviation of bone density above the peak average for a young woman; WHI, Women's Health Initiative.

Table 5. Cross-tabulation of Women With Osteoporosis Identified by DXA and Women's Health Initiative Algorithm

	No. of Women			No. (%) of Women With Hip Fracture Within 5 Years	
DXA	WHI Score <21	WHI Score ≥21	Total	WHI Score <21	WHI Score ≥21
T score ≥−2.5	9859	367	**10 226**	50 (0.51)	10 (2.72)
T score <−2.5	409	115	**524**	15 (3.67)	5 (4.35)
Total	**10 268**	**482**	**10 750**		

Abbreviations: DXA, dual-energy x-ray absorptiometry; T score, a standard deviation of the bone density above the peak average for a young woman; WHI, Women's Health Initiative.

Table 6. Women's Health Initiative Estimated Probability of Hip Fracture Within 5 Years by Women's Health Initiative Hand Score

	WHI Probability Score, %[a]		
WHI Hand Score[b]	2.5th Percentile	Median (50th Percentile)	97.5th Percentile
≤7	<0.1	<0.1	<0.1
8	<0.1	<0.1	0.1
9	<0.1	0.1	0.2
10	<0.1	0.1	0.2
11	<0.1	0.2	0.3
12	0.1	0.2	0.4
13	0.1	0.3	0.5
14	0.2	0.4	0.6
15	0.2	0.5	0.8
16	0.3	0.6	1.0
17	0.4	0.8	1.3
18	0.5	1.0	1.6
19	0.7	1.3	2.0
20	0.9	1.6	2.6
21	1.1	2.1	3.3
22	1.4	2.7	4.3
23	2.0	3.5	>5.0
24	2.8	4.6	>5.0
≥25	3.6	>5.0	>5.0

Abbreviation: WHI, Women's Health Initiative.
[a] WHI probability of hip fracture within 5 years based on WHI observational study.
[b] Simple sum score approximating WHI probability score.

COMMENT

The large sample size, multiethnic composition, geographically diverse, ambulatory population, and adjudicated hip fracture outcomes in WHI has made it possible to develop a comprehensive model to predict the 5-year risk of hip fracture in postmenopausal women. Because we were working from one dataset, with 93 676 postmenopausal women to develop the model and more than 60 000 women to validate it, our conclusions are robust. Because of the great uniformity in the collection methods and uniformity in the factors included in the model creation and validation testing, plus significant differences in the frequency of risk factors, the model appears to be generalizable.

Instead of splitting the sample to have a training set and a test set, we were able to take advantage of the multiple components of WHI, using one group to develop the model, the training set, and another to validate it, the validation set. By including minority women in the model, predicting fracture risk extends risk factors for nonwhite women beyond race or ethnic background.

Age is a known major risk factor for fracture and continues to be the most powerful predictor of fracture risk, but we have demonstrated that the addition of a few readily available items of clinical information can enhance this prediction. As with many prediction models, one is faced with a trade-off between specificity and sensitivity. As can be seen from Table 4, most fractures occur in women who are predicted to be a low risk. Figure 2 clearly demonstrates this trade off.

The comparison of the DXA prediction with the algorithm is limited by sample size, and there is no statistically significant difference even though within these limits, the DXA appears to give marginally better results at an obviously greater cost. But before the algorithm is considered definitive, these 2 methods should be tested in other large populations. The role of each needs to be clarified relative to screening and treatment.

There are a several limitations to this study. Certain data, such as accurate classification of arthritis type or an objective measure of physical activity were not available, but those factors that were available were clearly defined. Dual-energy x-ray absorptiometry data were not available for all participants; however, this model may provide a low-cost general screening prediction model that has certain advantages for general use. In addition, a longer period than 5 years might provide more information for long-term fracture prediction. Unfortunately, 5 years is the maximum follow-up available across the components of the study at this time. Other prediction models, eg, the Gail model for breast cancer, also has been predictive of breast cancer over more than 5 years. The cohort continues to be followed up and future assessment of longer-term prediction models may be available in the future.

Some aspects of the study may limit its generalizability to other populations. Of note, the annual hip fracture rate in women older than 65 years estimated from the 2004 National Hospital Discharge Survey is 57/10 000 women compared with rates of 30 in the observational and 32 in the clinical trial of women participating in the WHI who were in the same age group. This may reflect the higher BMI in the WHI population, the truncation of upper age groups and the healthy volunteer effect. In addition, the national data includes institutionalized women who have much higher fracture rates. Women in the training set and the validation set differ in many ways: for example, the validation set included more than 27 000 women in the hormone therapy clinical trials. Hormone therapy is known to greatly influence fracture risk, but hormone therapy was not selected as a useful predictor in the observational study training data. The model from the training data still appeared valid in the validation data. The lower risk of fracture in the WHI population may or may not be corrected by the factors in the model. The answer will only come when the model is tested in disparate populations.

This study does not indicate whether women defined by the WHI algorithm to be at risk would benefit from measures to prevent hip fracture in contrast to those trials that have used DEXA-T scores as a criterion for treatment. Some women who would be classified as high risk (point score >21) in our study did not have low T scores, which is currently used as the gold standard for defining osteoporosis. Further studies are needed to define the clinical implications of this algorithm and to confirm treatment benefits for those delineated by the WHI risk classification to be an increased risk for hip fracture. Ultimately, the decision of whom to further screen for osteoporosis and whom to treat will need to be based on available resources and major social and political judgments. Knowing the 5-year risk of fracture will permit patients and physicians to make informed choices when balancing making lifestyle changes against undergoing medical interventions. Publication of these results, along with the user-friendly tool for their application, will permit others to rapidly test their utility. However, we believe 11 readily available clinical variables offer a simple means of stratifying the 5-year risk of hip fracture in postmenopausal women.

Author Contributions: Dr Robbins had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Robbins, Kooperberg, Watts, Wactawski-Wende, Lewis, Chen, LeBoff.
Acquisition of data: Robbins, Kooperberg, Watts, Wactawski-Wende, Jackson, Lewis, Stefanick.
Analysis and interpretation of data: Aragaki, Kooperberg, Watts, Wactawski-Wende, Jackson, Chen, LeBoff, Stefanick, Cauley.
Drafting of the manuscript: Robbins, Aragaki, Kooperberg.
Critical revision of the manuscript for important intellectual content: Robbins, Aragaki, Kooperberg, Watts, Wactawski-Wende, Jackson, Lewis, Chen, LeBoff, Stefanick, Cauley.
Statistical analysis: Aragaki, Kooperberg, LeBoff.
Obtained funding: Robbins, Wactawski-Wende, Lewis, Stefanick.
Administrative, technical, or material support: Robbins, Kooperberg, Wactawski-Wende, Jackson, Lewis, LeBoff, Cauley.
Study supervision: Robbins, Kooperberg, Watts, Wactawski-Wende.

Financial Disclosures: Dr Cauley reports that she has received research support from Merck & Co, Eli Lilly & Co, Pfizer Pharmaceuticals, and Novartis Pharmaceuticals; has served as a consultant for Eli Lily and Novartis; and serves on the Merck speaker's bureau. No other financial conflicts were disclosed.

WHI Investigators: Program Office: National Heart, Lung, and Blood Institute, Elizabeth Nabel, Jacques Rossouw, Shari Ludlam, Linda Pottern, Joan McGowan, Leslie Ford, and Nancy Geller.
Clinical Coordinating Center: *Fred Hutchinson Cancer Research Center, Seattle, Wash:* Ross Prentice, Garnet Anderson, Andrea LaCroix, Charles L. Kooperberg, Ruth E. Patterson, Anne McTiernan; *Wake Forest University School of Medicine, Winston-Salem, North Carolina:* Sally Shumaker; *Medical Research Labs, Highland Heights, Kentucky:* Evan Stein; *University of California at San Francisco, San Francisco:* Steven Cummings.
Clinical Centers: *Albert Einstein College of Medicine, Bronx, New York:* Sylvia Wassertheil-Smoller; *Baylor College of Medicine, Houston, Texas:* Jennifer Hays; *Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts:* JoAnn Manson; *Brown University, Providence, Rhode Island:* Annlouise R. Assaf; *Emory University, Atlanta, Georgia:* Lawrence Phillips; *Fred Hutchinson Cancer Research Center, Seattle, Washington:* Shirley Beresford; *George Washington University Medical Center, Washington, DC:* Judith Hsia; *Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, California:* Rowan Chlebowski; *Kaiser Permanente Center for Health Research, Portland, Ore:* Evelyn Whitlock; *Kaiser Permanente Division of Research, Oakland, Calif:* Bette Caan; *Medical College of Wisconsin, Milwaukee:* Jane Morley Kotchen; *MedStar Research Institute/Howard University, Washington, DC:* Barbara V. Howard; *Northwestern University, Chicago/Evanston, Illinois:* Linda Van Horn; *Rush Medical Center, Chicago, Illinois:* Henry Black; *Stanford Prevention Research Center, Stanford, California:* Marcia L. Stefanick; *State University of New York at Stony Brook, Stony Brook:* Dorothy Lane; *The Ohio State University, Columbus:* Rebecca Jackson; *University of Alabama at Birmingham, Birmingham:* Cora E. Lewis; *University of Arizona, Tucson/Phoenix:* Tamsen Bassford; *University at Buffalo, Buffalo, New York:* Jean Wactawski-Wende; *University of California at Davis, Sacramento:* John Robbins; *University of California at Irvine:* F. Allan Hubbell; *University of California at Los Angeles, Los Angeles:* Howard Judd; *University of California at San Diego, LaJolla/Chula Vista:* Robert D. Langer; *University of Cincinnati, Cincinnati, Ohio:* Margery Gass; *University of Florida, Gainesville/Jacksonville:* Marian Limacher; *University of Hawaii, Honolulu:* David Curb; *University of Iowa, Iowa City/Davenport:* Robert Wallace; *University of Massachusetts/Fallon Clinic, Worcester:* Judith Ockene; *University of Medicine and Dentistry of New Jersey:* Norman Lasser; *University of Miami, Miami, Florida:* Mary Jo O'Sullivan; *University of Minnesota, Minneapolis:* Karen Margolis; *University of Nevada, Reno:* Robert Brunner; *University of North Carolina, Chapel Hill:* Gerardo Heiss; *University of Pittsburgh, Pittsburgh, Pennsylvania:* Lewis Kuller; *University of Tennessee, Memphis:* Karen C. Johnson; *University of Texas Health Science Center, San Antonio:* Robert Brzyski; *University of Wisconsin, Madison:* Gloria E. Sarto; *Wake Forest University School of Medicine, Winston-Salem, North Carolina:* Denise Bonds; and *Wayne State University School of Medicine/Hutzel Hospital, Detroit, Michigan:* Susan Hendrix.
Funding/Support: The Women's Health Initiative program was funded by the National Heart, Lung, and Blood Institute of the National Institutes of Health, Department of Health and Human Services.
Role of the Sponsor: The funding organization had representation on the steering committee, which gov-

erned the design and conduct of the study, the interpretation of the data, and the preparation and approval of manuscripts. The National Heart, Lung, and Blood Institute Program Office reviewed the manuscript prior to publication.

REFERENCES

1. National Center for Health Statistics. National Hospital Discharge and Ambulatory Surgery Data. http://www.cdc.gov/nchs/about/major/hdasd/nhdstab.htm. Accessed July 7, 2007.
2. Braithwaite RS, Col NF, Wong JB. Estimating hip fracture morbidity, mortality and costs. *J Am Geriatr Soc*. 2003;51(3):364-370.
3. Cummings SR, Nevitt MC, Browner WS, et al. Risk factors for hip fracture in white women: Study of Osteoporotic Fractures Research Group. *N Engl J Med*. 1995;332(12):767-773.
4. Black DM, Steinbuch M, Palermo L, et al. An assessment tool for predicting fracture risk in postmenopausal women. *Osteoporos Int*. 2001;12(7):519-528.
5. Buist DS, LaCroix AZ, Manfredonia D, Abbott T. Identifying postmenopausal women at high risk of fracture in populations: a comparison of three strategies. *J Am Geriatr Soc*. 2002;50(6):1031-1038.
6. McGrother CW, Donaldson MM, Clayton D, Abrams KR, Clarke M. Evaluation of a hip fracture risk score for assessing elderly women: the Melton Osteoporotic Fracture (MOF) study. *Osteoporos Int*. 2002;13(1):89-96.
7. van Staa TP, Leufkens HG, Cooper C. Utility of medical and drug history in fracture risk prediction among men and women. *Bone*. 2002;31(4):508-514.
8. Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *Eur J Epidemiol*. 1991;7(4):403-422.
9. Wainwright SA, Marshall LM, Ensrud KE, et al. Hip fracture in women without osteoporosis. *J Clin Endocrinol Metab*. 2005;90(5):2787-2793.
10. Fang J, Freeman R, Jeganathan R, Alderman MH. Variations in hip fracture hospitalization rates among different race/ethnicity groups in New York City. *Ethn Dis*. 2004;14(2):280-284.
11. Ritenbaugh C, Patterson RE, Chlebowski RT, et al. The Women's Health Initiative Dietary Modification trial: overview and baseline characteristics of participants. *Ann Epidemiol*. 2003;13(9)(suppl):S87-S97.
12. Stefanick ML, Cochrane BB, Hsia J, Barad DH, Liu JH, Johnson SR. The Women's Health Initiative postmenopausal hormone trials: overview and baseline characteristics of participants. *Ann Epidemiol*. 2003;13(9)(suppl):S78-S86.
13. Jackson RD, LaCroix AZ, Cauley JA, McGowan J. The Women's Health Initiative calcium-vitamin D trial: overview and baseline characteristics of participants. *Ann Epidemiol*. 2003;13(9)(suppl):S98-S106.
14. Design of the Women's Health Initiative clinical trial and observational study: The Women's Health Initiative Study Group. *Control Clin Trials*. 1998;19(1):61-109.
15. Curb JD, McTiernan A, Heckbert SR, et al. Outcomes ascertainment and adjudication methods in the Women's Health Initiative. *Ann Epidemiol*. 2003;13(9)(suppl):S122-S128.
16. Anderson GL, Manson J, Wallace R, et al. Implementation of the Women's Health Initiative study design. *Ann Epidemiol*. 2003;13(9)(suppl):S5-S17.
17. Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med*. 2006;354(7):669-683.
18. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA*. 2004;291(14):1701-1712.
19. Cauley JA, Robbins J, Chen Z, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *JAMA*. 2003;290(13):1729-1738.
20. Langer RD, White E, Lewis CE, Kotchen JM, Hendrix SL, Trevisan M. The Women's Health Initiative Observational Study: baseline characteristics of participants and reliability of baseline measures. *Ann Epidemiol*. 2003;13(9)(suppl):S107-S121.
21. Hays J, Hunt JR, Hubbell FA, et al. The Women's Health Initiative recruitment methods and results. *Ann Epidemiol*. 2003;13(9)(suppl):S18-S77.
22. Chen Z, Kooperberg C, Pettinger MB, et al. Validity of self-report for fractures among a multiethnic cohort of postmenopausal women: results from the Women's Health Initiative observational study and clinical trials. *Menopause*. 2004;11(3):264-274.
23. Hsia J, Wu L, Allen C, et al. Physical activity and diabetes risk in postmenopausal women. *Am J Prev Med*. 2005;28(1):19-25.
24. Wolf AM, Hunter DJ, Colditz GA, et al. Reproducibility and validity of a self-administered physical activity questionnaire. *Int J Epidemiol*. 1994;23(5):991-999.
25. Ainsworth BE, Haskell WL, Leon AS, et al. Compendium of physical activities: classification of energy costs of human physical activities. *Med Sci Sports Exerc*. 1993;25(1):71-80.
26. Andresen EM, Malmgren JA, Carter WB, Patrick DL. Screening for depression in well older adults: evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale). *Am J Prev Med*. 1994;10(2):77-84.
27. Patterson RE, Kristal AR, Tinker LF, Carter RA, Bolton MP, Agurs-Collins T. Measurement characteristics of the Women's Health Initiative food frequency questionnaire. *Ann Epidemiol*. 1999;9(3):178-187.
28. Neuhouser ML, Patterson RE, King IB, Horner NK, Lampe JW. Selected nutritional biomarkers predict diet quality. *Public Health Nutr*. 2003;6(7):703-709.
29. Stone M. Cross-Validatory Choice and Assessment of Statistical Predictions. *J R Stat Soc [Ser B]*. 1974;36(2):111-147.
30. Lloyd-Jones DM, Liu K, Tian L, Greenland P. Narrative review: assessment of C-reactive protein in risk prediction for cardiovascular disease. *Ann Intern Med*. 2006;145(1):35-42.
31. Kooperberg C. *polspline: Polynomial spline routines* [computer program]. R package version 1.0.14. 2007.
32. Sing T, Sander O, Beerenwinkel N, Lengauer T. ROCR: visualizing classifier performance in R. *Bioinformatics*. 2005;21(20):3940-3941.
33. R Development Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2007. http://www.R-project.org. Accessed November 6, 2007.

論文名	Factors associated with 5-year risk of hip fracture in postmenopausal women
著 者	Robbins J, Aragaki AK, Kooperberg C, Watts N, Wactawski-Wende J, Jackson RD, LeBoff MS, Lewis CE, Chen Z, Stefanick ML, Cauley J.
雑誌名	JAMA – the journal of the American Medical Association
巻・号・頁	298(20)　2389-2398
発行年	2007
PubMedリンク	http://www.ncbi.nlm.nih.gov/pubmed/18042916

対象の内訳	ヒト	動物	地 域	研究の種類
対象	一般健常者	空白	欧米	縦断研究
性別	女性	( )	( )	コホート研究
年齢	~79歳(平均64.5		( )	( )
対象数	10000以上		( )	前向きコホート ( )

調査の方法	質問紙	( )			
アウトカム 予 防	なし	なし	なし	転倒・骨折予防	( )
アウトカム 維持・改善	な し	な し	な し	なし	( )

図 表

Table 2. Multivariate Logistic Regression Model: Risk Factors for Hip Fracture in the Observational Study

Risk Factors	Odds Ratio (95% Confidence Interval)	*P* Value	Point Score
Age per each year	1.13 (1.11-1.15)	<.001	½ per year >50
Self-reported health			
Fair or poor vs excellent	2.38 (1.66-3.40)	<.001	3
Good vs excellent	1.22 (0.90-1.66)		1
Very good vs excellent	1.11 (0.83-1.49)		0
Height per each inch	1.11 (1.07-1.16)	<.001	½ per inch >64
Weight per each pound	0.99 (0.98-0.99)	<.001	1 per 25 lb <200
Fracture on or after age 55 y			
Not applicable vs no	1.01 (0.51-2.02)	<.001	0
Yes vs no	1.72 (1.41-2.10)		2
Race/ethnicity			White, 3
Unknown vs white	1.00 (0.47-2.14)	<.001	
Asian/Pacific Islander vs white	0.26 (0.10-0.70)		
American Indian vs white	1.60 (0.50-5.10)		
Hispanic vs white	0.32 (0.12-0.86)		
Black vs white	0.41 (0.24-0.70)		
Physical activity, METs			1
5-12 vs ≤12	1.32 (1.04-1.67)	.004	
<5 vs ≤12	1.26 (0.97-1.64)		
Inactive 0 vs ≤12	1.64 (1.24-2.17)		
Smoking status			
Current vs never	2.33 (1.71-3.18)	<.001	3
Past vs never	0.96 (0.79-1.17)		0
Parent broke hip, yes vs no	1.50 (1.20-1.87)	<.001	1
Corticosteroid use, yes vs no	1.94 (1.16-3.25)	.01	3
Use of hypoglycemic agent, yes vs no	1.74 (1.17-2.60)	.006	2

図表掲載箇所	P2393, Table2
概 要 (800字まで)	本研究はWomen's Health initiativeに参加している閉経後女性92,629名を対象に、7.6年間の追跡調査を行い、腰部骨折に対する予測を行うためのアルゴリズムを開発することを目的に行っている。腰部骨折を予測した因子は、年齢、自己申告の健康、体重、身長、人種、自己申告による身体活動、54歳以上での骨折歴、腰部骨折の家族歴、喫煙、副腎皮質ステロイドの使用、治療中の糖尿病の11項目であった。自己申告による身体活動量により、身体活動量が12メッツ・時/週以上、5-12メッツ・時/週、0.1-4.9メッツ・時/週、実施せずに分類した場合、腰部骨折のリスクは、それぞれ、1.0、1.32(1.04-1.67)、1.26(0.97-1.64)、1.64(1.24-2.17)であり、身体活動量が減少するに伴い、腰部骨折のリスクが上昇していた。上記の11項目を用いたアルゴリズムによる腰部骨折の予測をROC(Receiver operating characteristic)曲線により検討したところ、area under curveは80%を示した(95%CI;: 0.77-0.82)。
結 論 (200字まで)	11項目の要因を用いたアルゴリズムを用いることで閉経後女性の腰部骨折のリスクを予測することが可能である。
エキスパートによるコメント (200字まで)	骨折は、高齢者における寝たきりの重大な要因である。これらを予測することが可能になることで、ハイリスク者を特定し、より重点的な支援につなげることが可能となり、非常に有意義な研究であるといえる。また身体活動に関しては、12メッツ・時/週を下回らないことが腰部骨折のリスク減少に重要である。

担当者　村上晴香

A Follow-up Study of Physical Activity and Incidence of Colorectal Polyps in African-American Women

Lynn Rosenberg,[1] Deborah Boggs,[1] Lauren A. Wise,[1] Julie R. Palmer,[1] Mark H. Roltsch,[2] Kepher H. Makambi,[3] and Lucile L. Adams-Campbell[3]

[1]Slone Epidemiology Center, Boston University, Boston, Massachusetts; [2]National Heart, Lung, and Blood Institute, Bethesda, Maryland; and [3]Howard University Cancer Center, Washington, District of Columbia

Abstract

Background: **Physical activity is associated with a reduced risk of colon cancer, but the effect of activity on colorectal adenomas, which are precursors to colon cancer, is uncertain. The influence of physical activity on colorectal adenomas among African-American women is of particular interest because African-American women have an increased risk of colon cancer relative to other U.S. women.**

Methods: **We prospectively assessed the relation of physical activity to the incidence of colorectal polyps among African-American women. We followed 45,400 women in the Black Women's Health Study from 1997 to 2003. Data were obtained by biennial mailed questionnaires. During 287,029 person-years of follow-up, 1,390 women reported having been diagnosed with colorectal polyps. A review of medical records of 58 women who reported colorectal polyps indicated that 59% had adenomas and 41% had hyperplastic polyps. We converted hours per week of vigorous exercise and hours per week of walking to metabolic equivalent (MET)-hours. We estimated incidence rate ratios with Cox proportional hazard models, controlling for age, body mass index, smoking, family history of colorectal cancer, and education.**

Results: **For total MET-hours/wk spent in walking and vigorous exercise, the incidence rate ratio decreased from 0.94 for <5 MET-hours/wk to 0.72 for ≥40 MET-hours/wk (P_{trend} = 0.01). The inverse association was apparent among most subgroups examined, including women who may be at higher risk of colorectal adenomas because of being obese.**

Conclusions: **Increased physical activity is associated with a reduced incidence of colorectal polyps among African-American women.** (Cancer Epidemiol Biomarkers Prev 2006; 15(8):1438–42)

Introduction

An appreciable body of evidence suggests that leisure-time physical activity reduces the incidence of colon cancer in men and women (1, 2). There is much less evidence on whether physical activity protects against colorectal adenomas, which are thought to be precursors to most colon cancers (3), and the evidence has been inconsistent (4-17). No findings have been reported on the relation of physical activity to the incidence of colorectal adenomas in African-American women. This is an issue of particular interest because incidence and mortality rates of colorectal cancer are greater among African-American women than among U.S. white women (18). We report here on the effect of leisure-time physical activity on the incidence of colorectal polyps in African-American women. It has been estimated that about three quarters of clinically recognized polyps are adenomas and one quarter are hyperplastic polyps (19). We used data from the Black Women's Health Study (BWHS), a large follow-up study of black women in the United States.

Materials and Methods

The BWHS began in 1995 when 59,000 African-American women ages 21 to 69 years enrolled in the study by completing mailed health questionnaires (20). Most respondents were subscribers to Essence magazine, a popular magazine targeted to black women; the remainder were members of the Black Nurses' Association or the National Education Association or were friends and relatives of early respondents. Twenty-seven percent of respondents lived in the Northeast, 29% in the South, 23% in the Midwest, and 21% in the West. Participants are followed through biennial mailed questionnaires. The present report is based on data collected through 2003. Each of the 1997, 1999, 2001, and 2003 follow-up questionnaires was completed by ≥80% of the original cohort; 2% of the cohort had died by 2003. The Institutional Review Boards of Boston University Medical Center (Boston, MA) and Howard University Cancer Center (Washington, DC) approved the BWHS.

Colorectal Polyps. The 1995 baseline questionnaire and the follow-up questionnaires through 2003 included questions about a list of illnesses that included colon and rectal cancer. In 1999, colorectal polyps were added to the list; on that questionnaire and all subsequent questionnaires, participants were asked if they had been diagnosed with "colon or rectal polyps" and the year of first diagnosis. Because colorectal polyps were not asked about specifically until 1999, we began follow-up for the present analyses in 1997.

In a sample of 63 BWHS participants who reported colorectal polyps on the 2001 questionnaire and for whom we obtained medical records, colorectal polyps were confirmed in 58 (92%). Among the 58 participants, 34 (59%) had adenomas and 24 (41%) had hyperplastic polyps.

Physical Activity. Physical activity data from the 1997, 1999, and 2001 questionnaires were used for the present analyses. All questionnaires through 2001 collected information on the average number of hours per week in the previous year that the participant had walked for exercise, had walked to and from work, stores, church, and school, and had exercised vigorously (e.g., running). We estimated total metabolic equivalent (MET)-hours/wk from walking

Received 2/12/06; revised 5/17/06; accepted 6/1/06.

Grant support: National Cancer Institute grant CA58420.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Requests for reprints: Lynn Rosenberg, Slone Epidemiology Center, Boston University, 1010 Commonwealth Avenue, Boston, MA 02215. Phone: 617-734-6006; Fax: 617-738-5119. E-mail: lrosenberg@slone.bu.edu

doi:10.1158/1055-9965.EPI-06-0079

and vigorous exercise by summing the MET-hours/wk from walking (hours per week multiplied by 3.5) and the MET-hours/wk from vigorous exercise (hours per week multiplied by 7.0; ref. 21).

In a validation study conducted at Howard University Cancer Center, 101 BWHS participants wore actigraphs (activity monitors) for 7 days during their waking hours. They also completed physical activity diaries and the BWHS questions about physical activity. Hours per week of physical activity from walking and vigorous exercise reported on the BWHS questionnaire and in the diary were converted to MET-hours/wk by multiplying the hours per week of walking by 3.5 and the hours per week of vigorous exercise by 7.0; total physical activity was the sum of the MET-hours from walking and vigorous exercise. For total physical activity, the Spearman correlation coefficient was 0.28 ($P < 0.01$) for the correlation of the BWHS questionnaire data with the actigraph counts and 0.32 ($P < 0.01$) for the correlation of the questionnaire data with the diary data. For vigorous exercise, the corresponding correlation coefficients were 0.40 ($P < 0.01$) and 0.41 ($P < 0.01$).

Other Factors. The baseline and follow-up questionnaires collected information on a wide range of health-related factors, such as cigarette smoking and alcohol use. All questionnaires collected information on weight, and the 1995 questionnaire collected information on height, allowing for the computation of body mass index (BMI; kg/m^2). The 1995 questionnaire included a 68-item modification of the short version of the National Cancer Institute/Block food frequency questionnaire (22); nutrient estimates were derived using the DietSys software version 3.7 (National Cancer Institute, Bethesda, MD). The 1999 questionnaire asked about family history of colon cancer and rectal cancer and about whether the participant had undergone colonoscopy or sigmoidoscopy in the previous 2 years. The 2003 questionnaire asked about colonoscopy and sigmoidoscopy in the previous 2 years.

Analysis. We assessed colorectal polyps occurring in a particular follow-up cycle in relation to exposure data from the previous cycle (e.g., polyps reported on the 1999 questionnaire in relation to physical activity reported on the 1997 questionnaire). A total of 53,176 women completed the 1997 follow-up questionnaire, the start of follow-up for the present analyses. After exclusion of women who had cancer at baseline (n = 1,467), reported colorectal polyps occurring before 1997 (n = 537), did not complete a follow-up questionnaire after 1997 (3,112), did not complete the 1997 questions on physical activity (2,612), or whose status with respect to colorectal polyps was uncertain (n = 48), a total of 45,400 women remained. During 287,029 person-years of follow-up from 1997 to 2003, 1,390 of these women reported the occurrence of a colorectal polyp.

We used age- and time-stratified Cox regression models (Statistical Analysis System version 8.2, SAS Institute, Cary, NC) to derive incidence rate ratios (IRR) for colorectal polyps in relation to physical activity with control for potential confounding factors (23). Women contributed person-years from the start of follow-up in 1997 to the time of diagnosis of colorectal polyps, loss to follow-up, death, or the end of follow-up in 2003, whichever came first. In the analyses of total MET-hours from walking and vigorous activity, we controlled for known or suspected risk factors for colorectal polyps that were associated with risk of polyps in our data; in addition to age, these were BMI [weight (kg)/height^2 (m)], cigarette smoking, history of colorectal cancer in a parent or sibling, and years of education. In the analysis of hours per week of walking, we also controlled for vigorous activity; in the analysis of hours per week of vigorous activity, we also controlled for walking. Additional control for geographic region of residence, alcohol use, nonsteroidal anti-inflammatory drug use, red meat intake, fiber intake, and total energy intake did not alter the IRRs by >10%. The Anderson-Gill data structure was used to handle time-varying covariates (24).

To test for trend among women who walked or exercised vigorously, a continuous term was included in the regression model and those reporting no activity were excluded; for hours per week of walking or vigorous exercise, the midpoint of each stratum of hours/week of activity reported was used. To assess whether the association between MET-hours of physical activity and colorectal polyps was modified by other factors (e.g., BMI), we conducted likelihood ratio tests that compared models with and without cross-product terms between MET-hours of physical activity (categorical) and these factors (25). Departure from the proportional hazards assumption was tested by the likelihood ratio test comparing models with and without cross-product terms between MET-hours of physical activity (categorical), time period, and age (<50 versus ≥50; ref. 26).

Results

Age, BMI, cigarette smoking, family history of colorectal cancer, and years of education were positively associated with the incidence of colorectal polyps in the BWHS (data not shown). As shown in Table 1, total MET-hours/wk expended in walking and vigorous exercise were positively associated with years of education and inversely associated with age, BMI, smoking, and family history of colorectal cancer.

Table 2 provides data on vigorous exercise and walking in relation to colorectal polyp incidence. For women who exercised vigorously relative to women who did no vigorous exercise, the IRRs were all <1.0 for categories of vigorous exercise ranging from <1 hour/wk to ≥7 hours/wk: the IRR was 0.81 [95% confidence interval (95% CI), 0.69-0.96] for <1 hour/wk and 0.85 (95% CI, 0.60-1.21) for ≥7 hours/wk (P_{trend} among vigorous exercisers = 0.54). For walking, the IRRs were 0.99 or 1.00 for the categories <1 hour/wk to 3 to 4 hours/wk and 0.82 and 0.85 for 4 to 6 hours/wk and ≥7 hours/wk, respectively (P_{trend} among walkers = 0.03); all 95% CI included 1.0. For total MET-hours/wk expended in walking and vigorous exercise, the IRR decreased monotonically from 0.94 (95% CI, 0.76-1.15) for <5 MET-hours/wk to 0.83 (95% CI, 0.67-1.03) for 20 to 39 MET-hours/wk and 0.72 (95% CI, 0.57-0.91) for ≥40 MET-hours/wk (P_{trend} among the walkers and exercisers = 0.01).

We repeated the analysis of total MET-hours/wk from walking and vigorous exercise in relation to colorectal polyps confined to women who reported on the 1999 or 2003 questionnaire that they had undergone sigmoidoscopy or colonoscopy. Based on 63,302 person-years of follow-up involving 10,079 women, the IRRs for the categories of total MET-hours/wk of <5, 5 to 9, 10 to 19, 20 to 39, and ≥40, relative to none, were 0.88 (95% CI, 0.72-1.09), 0.86 (95% CI, 0.70-1.06), 0.85 (95% CI, 0.69-1.04), 0.76 (95% CI, 0.61-0.95), and 0.64 (95% CI, 0.50-0.81), respectively.

Table 1. Baseline characteristics of 45,381 women according to MET-hours/wk of vigorous exercise and walking in the BWHS

Characteristic	MET-h/wk				
	<5	5-9	10-19	20-39	≥40
No. studied	10,984	8,188	10,117	8,782	7,329
Age, y (mean)	42.2	40.9	40.7	39.4	38.7
BMI, kg/m^2 (mean)	29.8	28.9	28.4	27.5	27.0
Education, y (mean)	14.6	14.9	15.0	15.1	15.0
Family history of colorectal cancer (%)	5.8	6.2	5.9	5.4	5.4
Current smoker (%)	18.2	14.6	14.3	13.1	14.8

As shown in Table 3, the IRR for ≥40 MET-hours/wk of physical activity spent in walking and vigorous exercise was <1.0 in all categories of age, BMI, family history of colorectal cancer, cigarette smoking, and years of educational attainment, except among the subgroups of women with BMI 25 to 29 and ≤12 years of education. None of the tests for interaction was statistically significant (age, P = 0.22; BMI, P = 0.41; family history of colorectal cancer, P = 0.56; cigarette smoking, P = 0.62; education, P = 0.38).

Discussion

The results from studies of physical activity and colorectal adenomas have been mixed and inconclusive. Among the case-control studies (4, 7-17), most were small with ≤300 adenoma cases (4, 7-9, 11, 13-17), and statistically significant inverse associations were found in only 2 (16, 17). In a follow-up of nurses who had undergone endoscopy, during which 439 adenomas of the distal colorectum were reported, the IRR was 0.58 (95% CI 0.40-0.86) for the highest quintile of weekly energy expenditure from walking and exercise relative to the lowest (P_{trend} = 0.0009; ref. 5). In a similar follow-up study of men, in which 586 adenomas were reported, there were also inverse associations, although weaker: the relative risk for the top quintile of energy expenditure relative to the lowest was 0.79 (P_{trend} = 0.12) for colon adenomas and 0.92 (P_{trend} = 0.55) for rectal adenomas (6).

The present study provides the first data on physical activity in relation to colorectal polyps specifically reported for a black population. The incidence of polyps among black women in the BWHS declined as total MET-hours expended in walking and vigorous exercise increased. A reduction in incidence of ~20% was associated with 20 to 39 MET-hours/wk of physical activity and of 30% with ≥40 MET-hours/wk. Age, BMI, cigarette smoking, family history of colorectal cancer, and higher level of education were associated with increased risk of colorectal polyps in our data. Physical activity was inversely associated with the incidence of colorectal polyps in almost all strata of these factors, which suggests that these factors did not explain or modify the association of physical activity with colorectal polyps. The inverse association of physical activity with polyps among obese women is noteworthy because the risk of developing adenomatous polyps may be greater among people who are obese (4-6, 9, 11, 15, 16, 27).

The large number of cases of colorectal polyps in the present study provided high statistical power and allowed for informative assessment of subgroups. The high rate of follow-up mitigates concerns about bias from selective losses. Multivariable analyses controlled for important risk factors for colorectal polyps. Physical activity reported on the BWHS questionnaire was statistically significantly associated with two commonly used, albeit imperfect, measures that have been used in physical activity validation studies—diary record data and movement as measured with an actigraph (28, 29). Because the BWHS questionnaire data on physical activity were collected prospectively, systematic bias in the reporting of physical activity will have been absent. Random misclassification of reported physical activity on the BWHS questionnaire would have tended to attenuate a true inverse association between physical activity and the incidence of colorectal polyps.

Our validation study suggested that women in the BWHS reported colorectal polyps with high specificity. However, participants were not systematically screened for colorectal polyps. The presence of undetected cases of colorectal polyps would have attenuated an association, but we expect the degree of attenuation to have been small because colorectal polyps occur relatively rarely. An analysis confined to women who had undergone colonoscopy or sigmoidoscopy yielded an inverse association with total MET-hours of activity from walking and vigorous exercise that was a little stronger than that observed in the total sample.

We were unable to stratify the analyses according to whether the colorectal polyp was an adenoma or a hyperplastic polyp because we had that information on only a small subset of cases. Hyperplastic polyps are not thought to be risk factors for colon cancer. Although colon adenomas and hyperplastic polyps share many risk factors (30, 31), there is almost no information on the relation of hyperplastic polyps to

Table 2. Risk of colorectal polyps in relation to hours per week of vigorous exercise, hours per week of walking, and MET-hours/wk of vigorous exercise and walking in the BWHS

	Hours/wk of vigorous exercise					
	None	<1	1-2	3-4	5-6	≥7
Cases	875	181	173	88	39	34
Person-years	139,733	51,070	44,437	28,163	12,355	11,271
Age-adjusted IRR (95% CI)	1.00 (Reference)	0.80 (0.68-0.94)	0.92 (0.78-1.08)	0.74 (0.60-0.93)	0.81 (0.59-1.11)	0.77 (0.55-1.09)
Multivariate IRR* (95% CI)	1.00 (Reference)	0.81 (0.69-0.96)	0.95 (0.80-1.12)	0.77 (0.62-0.97)	0.87 (0.63-1.20)	0.85 (0.60-1.21)
	Hours/wk of walking					
	None	<1	1-2	3-4	5-6	≥7
Cases	153	230	496	235	108	168
Person-years	27,837	44,170	101,484	47,450	25,594	40,494
Age-adjusted IRR (95% CI)	1.00 (Reference)	0.99 (0.81-1.22)	0.96 (0.80-1.15)	0.94 (0.77-1.15)	0.78 (0.61-1.00)	0.79 (0.63-0.98)
Multivariate IRR† (95% CI)	1.00 (Reference)	1.00 (0.82-1.23)	1.00 (0.83-1.20)	0.99 (0.81-1.22)	0.82 (0.63-1.05)	0.85 (0.68-1.06)
	MET-h/wk of vigorous exercise and walking					
	None	<5	5-9	10-19	20-39	≥40
Cases	132	288	273	325	229	143
Person-years	20,793	49,475	53,541	64,706	55,242	43,272
Age-adjusted IRR (95% CI)	1.00 (Reference)	0.93 (0.76-1.15)	0.89 (0.72-1.10)	0.90 (0.74-1.10)	0.82 (0.66-1.01)	0.70 (0.55-0.88)
Multivariate IRR‡ (95% CI)	1.00 (Reference)	0.94 (0.76-1.15)	0.91 (0.74-1.12)	0.91 (0.74-1.12)	0.83 (0.67-1.03)	0.72 (0.57-0.91)

*Adjusted for age, BMI, smoking, family history of colorectal cancer, education, and total hours of walking.
†Adjusted for age, BMI, smoking, family history of colorectal cancer, education, and hours of vigorous exercise.
‡Adjusted for age, BMI, smoking, family history of colorectal cancer, and education.

Table 3. Risk of colorectal polyps in relation to MET-hours/wk of vigorous exercise and walking according to age, BMI, family history of colorectal cancer, cigarette smoking, and years of educational attainment in the BWHS

MET-h/wk	Age			
	<50		≥50	
	Cases	IRR (95% CI)	Cases	IRR (95% CI)
None	57	1.00	75	1.00
<5	100	0.75 (0.54- 1.05)	188	1.07 (0.82- 1.40)
5-9	109	0.78 (0.56- 1.07)	164	1.00 (0.76- 1.31)
10-19	133	0.80 (0.59- 1.10)	192	0.99 (0.76- 1.30)
20-39	95	0.68 (0.49- 0.95)	134	0.95 (0.71- 1.27)
≥40	60	0.57 (0.40- 0.83)	83	0.84 (0.62- 1.16)

MET-h/wk	BMI					
	<25		25-29		≥30	
	Cases	IRR (95% CI)	Cases	IRR (95% CI)	Cases	IRR (95% CI)
None	24	1.00	30	1.00	77	1.00
<5	49	0.97 (0.59-1.58)	94	1.22 (0.81-1.85)	140	0.78 (0.59-1.04)
5-9	58	1.02 (0.63-1.66)	107	1.28 (0.85-1.92)	106	0.68 (0.51-0.92)
10-19	69	0.96 (0.60-1.54)	125	1.16 (0.78-1.73)	128	0.77 (0.58-1.03)
20-39	71	1.04 (0.65-1.67)	91	1.07 (0.70-1.62)	66	0.60 (0.43-0.83)
≥40	34	0.59 (0.35-1.01)	62	1.02 (0.66-1.59)	42	0.63 (0.43-0.92)

MET-h/wk	Family history of colorectal cancer			
	Yes		No	
	Cases	IRR (95% CI)	Cases	IRR (95% CI)
None	21	1.00	105	1.00
<5	39	0.67 (0.39-1.14)	241	0.98 (0.78-1.24)
5-9	45	0.76 (0.45-1.29)	219	0.92 (0.73-1.16)
10-19	57	0.78 (0.46-1.30)	246	0.88 (0.70-1.11)
20-39	30	0.52 (0.29-0.92)	186	0.87 (0.68-1.11)
≥40	24	0.59 (0.33-1.09)	113	0.73 (0.56-0.95)

METs/wk	Smoking status			
	Current smoker		Past/never smoker	
	Cases	IRR (95% CI)	Cases	IRR (95% CI)
None	38	1.00	94	1.00
<5	52	0.78 (0.51-1.20)	236	1.00 (0.78-1.27)
5-9	51	0.83 (0.54-1.27)	222	0.93 (0.73-1.18)
10-19	56	0.82 (0.54-1.25)	269	0.95 (0.75-1.20)
20-39	33	0.65 (0.40-1.04)	196	0.89 (0.69-1.14)
≥40	30	0.80 (0.49-1.30)	113	0.72 (0.54-0.95)

MET-h/wk	Education (y)					
	≤12		13-15		≥16	
	Cases	IRR (95% CI)	Cases	IRR (95% CI)	Cases	IRR (95% CI)
None	24	1.00	54	1.00	54	1.00
<5	45	1.04 (0.63-1.71)	115	0.92 (0.66-1.27)	128	0.91 (0.66-1.25)
5-9	45	1.21 (0.74-2.00)	92	0.77 (0.55-1.09)	134	0.90 (0.66-1.24)
10-19	56	1.41 (0.87-2.29)	108	0.79 (0.57-1.10)	158	0.87 (0.64-1.19)
20-39	25	0.94 (0.53-1.65)	73	0.73 (0.51-1.04)	131	0.87 (0.63-1.20)
≥40	25	1.25 (0.71-2.20)	51	0.66 (0.45-0.97)	64	0.64 (0.44-0.92)

NOTE: In the analysis of each factor, adjustment is made for the other factors in this table.

physical activity. A study that assessed subsequent polyp occurrence among subjects who had had a recent colon adenoma found that physical activity was unrelated to hyperplastic polyps, but the number of cases was small (14). If hyperplastic polyps are unrelated to physical activity, their inclusion in the case series in the present study would have diluted the association of colorectal polyps with physical activity.

In summary, the present data suggest a protective effect of physical activity against the occurrence of colorectal polyps in black women. Colorectal cancer is a much rarer outcome than colorectal polyps (3, 5, 18). The assessment of whether physical activity protects against colon or rectal cancer in black women in the BWHS awaits accrual of sufficient cases of colon and rectal cancer for informative analysis.

Acknowledgments

We thank the participants in the BWHS for making this work possible.

References

1. Slattery M. Physical activity and colorectal cancer. Sports Med 2004;34:239–52.
2. Friedenreich CM, Orenstein MR. Physical activity and cancer prevention: etiologic evidence and biological mechanisms. J Nutr 2002;132:3456–64S.
3. Hill MJ, Morson BC, Bussey HJ. Aetiology of adenoma-carcinoma sequence in large bowel. Lancet 1978;1:245–7.
4. Terry MB, Neugut AI, Bostick RM, et al. Risk factors for advanced colorectal adenomas: a pooled analysis. Cancer Epidemiol Biomarkers Prev 2002;11: 622–9.
5. Giovannucci E, Colditz GA, Stampfer MJ, Willett WC. Physical activity, obesity, and risk of colorectal adenoma in women (United States). Cancer Causes Control 1996;7:253–63.
6. Giovannucci E, Ascherio A, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Physical activity, obesity, and risk for colon cancer and adenoma in men. Ann Intern Med 1995;122:327–34.
7. Neugut AI, Terry MB, Hocking G, et al. Leisure and occupational physical activity and risk of colorectal adenomatous polyps. Int J Cancer 1996;68: 744–8.
8. Little J, Logan RF, Hawtin PG, Hardcastle JD, Turner ID. Colorectal adenomas and energy intake, body size, and physical activity: a case-control study of subjects participating in the Nottingham faecal occult blood screening programme. Br J Cancer 1993;67:172–6.
9. Guilera M, Connelly-Frost A, Keku TO, Martin FM, Galanko J, Sandler RS. Does physical activity modify the association between body mass index and colorectal adenomas? Nutr Cancer 2005;5:140–5.
10. Enger SM, Longnecker MP, Lee ER, Frankl HD, Haile RW. Recent and past physical activity and prevalence of colorectal adenomas. Br J Cancer 1997;75: 740–5.
11. Boutron-Ruault MC, Senesse P, Meance S, Belghiti C, Faivre J. Energy intake, body mass index, physical activity, and the colorectal adenoma-carcinoma sequence. Nutr Cancer 2001;39:50–7.
12. Lieberman DA, Prindiville S, Weiss DG, Willett W. Risk factors for advanced colonic neoplasia and hyperplastic polyps in asymptomatic individuals. JAMA 2003;290:2959–67.
13. Hauret KG, Bostick RM, Matthews CE, et al. Physical activity and reduced risk of incident sporadic colorectal adenomas: observational support for mechanisms involving energy balance and inflammation modulation. Am J Epidemiol 2004;159:983–92.
14. Wallace K, Baron JA, Karagas MR, et al. The association of physical activity and body mass index with the risk of large bowel polyps. Cancer Epidemiol Biomarkers Prev 2005;14:2082–6.
15. Kono S, Handa K, Hayabuchi H, et al. Obesity, weight gain, and risk of colon adenomas in Japanese men. Jpn J Cancer Res 1999;90:805–11.
16. Lubin F, Rozen P, Arieli B, et al. Nutritional and lifestyle habits and water-fiber interaction in colorectal adenoma etiology. Cancer Epidemiol Biomarkers Prev 1997;6:79–85.
17. Sandler RS, Pritchard ML, Bangdiwala SI. Physical activity and the risk of colorectal adenomas. Epidemiology 1995;6:602–6.
18. U.S. Cancer Statistics. Web-based incidence and mortality reports 1999–2001; 1995. Available from: http://www.cdc.gov/cancer/npcr/uscs.
19. Ulrich CM, Kampman E, Bigler J, et al. Lack of association between the C677T MTHFR polymorphism and colorectal hyperplastic polyps. Cancer Epidemiol Biomarkers Prev 2000;9:427–33.
20. Rosenberg L, Adams-Campbell L, Palmer JR. The Black Women's Health Study: a follow-up study for causes and preventions of illness. J Am Med Womens Assoc 1995;50:56–8.
21. Ainsworth BE, Haskell WL, Leon AS, et al. Compendium of physical activities: classification of energy costs of human physical activities. Med Sci Sports Exerc 1993;25:71–80.
22. Block G, Hartman AM, Naughton D. A reduced dietary questionnaire: development and validation. Epidemiology 1990;1:58–64.
23. Cox DR, Oakes D. Analysis of survival data. London: Chapman Hall; 1984.
24. Therneau T. Extending the Cox model. In: Lin DY, Fleming TR, editors. Proceedings of the first Seattle symposium in biostatistics: survival analysis. New York: Springer Verlag; 1997. p. 51–84.
25. Breslow NE, Day NE. Statistical methods in cancer research, vol II. The design and analysis of cohort studies. Lyon (France): IARC; 1987.
26. Therneau TM, Grambsch PM. Modeling survival data: extending the Cox model. New York: Springer-Verlag; 2000.
27. Neugut AI, Lee WC, Garbowski GC, et al. Obesity and colorectal adenomatous polyps. J Natl Cancer Inst 1991;83:359–61.
28. Miller DJ, Freedson PS, Kline GM. Comparison of activity levels using the Caltrac accelerometer and five questionnaires. Med Sci Sports Exerc 1994;26: 376–82.
29. Jacobs DR, Jr., Ainsworth BE, Hartman TJ, Leon AS. A simultaneous evaluation of 10 commonly used physical activity questionnaires. Med Sci Sports Exerc 1993;25:81–91.
30. Martinez ME, McPherson RS, Levin B, Glober GA. A case-control study of dietary intake and other lifestyle risk factors for hyperplastic polyps. Gastroenterology 1997;113:423–9.
31. Kearney J, Giovannucci E, Rimm EB, et al. Diet, alcohol, and smoking and the occurrence of hyperplastic polyps of the colon and rectum (United States). Cancer Causes Control 1995;6:45–56.

論文名	A follow-up study of physical activity and incidence of colorectal polyps in African-American women
著 者	Rosenberg L, Boggs D, Wise LA, Palmer JR, Roltsch MH, Makambi KH, Adams-Campbell LL.
雑誌名	Cancer Epidemiol Biomarkers Prev.
巻・号・頁	15 8 1438-1442
発行年	2006
PubMedリンク	http://www.ncbi.nlm.nih.gov/pubmed/16896029

対象の内訳	ヒト	動物	地 域	欧米	研究の種類	縦断研究
対象	一般健常者	空白		( )		コホート研究
性別	女性	( )		( )		( )
年齢	21～69才(40歳)	[redacted]		( )		前向きコホート
対象数	10000以上			( )		( )
調査の方法	質問紙	( )				
アウトカム 予 防	なし	なし	ガン予防	なし		( )
アウトカム 維持・改善	なし	なし	なし	なし	(	( )

図 表

Table 2. Risk of colorectal polyps in relation to hours per week of vigorous exercise, hours per week of walking, and MET-hours/wk of vigorous exercise and walking in the BWHS

	Hours/wk of vigorous exercise					
	None	<1	1-2	3-4	5-6	≥7
Cases	875	181	173	88	39	34
Person-years	139,733	51,070	44,437	28,163	12,355	11,271
Age-adjusted IRR (95% CI)	1.00 (Reference)	0.80 (0.68-0.94)	0.92 (0.78-1.08)	0.74 (0.60-0.93)	0.81 (0.59-1.11)	0.77 (0.55-1.09)
Multivariate IRR* (95% CI)	1.00 (Reference)	0.81 (0.69-0.96)	0.95 (0.80-1.12)	0.77 (0.62-0.97)	0.87 (0.63-1.20)	0.85 (0.60-1.21)
	Hours/wk of walking					
	None	<1	1-2	3-4	5-6	≥7
Cases	153	230	496	235	108	168
Person-years	27,837	44,170	101,484	47,450	25,594	40,494
Age-adjusted IRR (95% CI)	1.00 (Reference)	0.99 (0.81-1.22)	0.96 (0.80-1.15)	0.94 (0.77-1.15)	0.78 (0.61-1.00)	0.79 (0.63-0.98)
Multivariate IRR† (95% CI)	1.00 (Reference)	1.00 (0.82-1.23)	1.00 (0.83-1.20)	0.99 (0.81-1.22)	0.82 (0.63-1.05)	0.85 (0.68-1.06)
	MET-h/wk of vigorous exercise and walking					
	None	<5	5-9	10-19	20-39	≥40
Cases	132	288	273	325	229	143
Person-years	20,793	49,475	53,541	64,706	55,242	43,272
Age-adjusted IRR (95% CI)	1.00 (Reference)	0.93 (0.76-1.15)	0.89 (0.72-1.10)	0.90 (0.74-1.10)	0.82 (0.66-1.01)	0.70 (0.55-0.88)
Multivariate IRR‡ (95% CI)	1.00 (Reference)	0.94 (0.76-1.15)	0.91 (0.74-1.12)	0.91 (0.74-1.12)	0.83 (0.67-1.03)	0.72 (0.57-0.91)

*Adjusted for age, BMI, smoking, family history of colorectal cancer, education, and total hours of walking.
†Adjusted for age, BMI, smoking, family history of colorectal cancer, education, and hours of vigorous exercise.
‡Adjusted for age, BMI, smoking, family history of colorectal cancer, and education.

図表掲載箇所	
概 要 (800字まで)	<目的>身体活動は大腸がんの低い危険性と関係している。しかし、結腸直腸ポリープ(大腸がんの前兆)に対する効果は不確かなので、それを検討した。<方法>コホート名:the Black Women's Healht Study、対象者数:45400人、追跡期間:6.3年、身体活動量評価方法詳細:直近の1年間に1週当たりにどれだけ歩いたか(メッツ3.5)と活発に運動したか(7メッツ)の時間を聞いた。身体活動量の単位:メッツ時/週。身体活動量で6分位に分類した。各分位の身体活動量は、分位1:なし、分位2:0-5メッツ・時/週、分位3:5-9メッツ・時/週、分位4:10-19メッツ・時/週、分位5:20-39メッツ・時/週、分位6:40メッツ・時/週以上であった。身体活動量と大腸ポリープ発生リスクは、分位1:1、分位2:0.94(0.76-1.15)、分位3:0.91(0.74-1.12)、分位4:0.91(0.74-1.12)、分位5:0.83(0.67-1.03)、分位6:0.72(0.57-0.91)であった。
結 論 (200字まで)	アメリカの黒人女性を対象に大腸のポリープ(腺腫)の発生をみた。総身体活動量は週40メッツ・時/週以上で大腸のポリープ(腺腫)の発生リスクの低下が有意となったが、歩行では1週間7時間、運動では1時間以上で有意であった。
エキスパートによるコメント (200字まで)	がんの発症でなく、その前駆段階であるポリープ形成と身体活動との関係を見た、一次予防的には極めて有用な研究である。

担当者 宮地元彦

DOI:10.1158/1055-9965.EPI-08-0042

Physical Activity, White Blood Cell Count, and Lung Cancer Risk in a Prospective Cohort Study

Brian L. Sprague,[1,3] Amy Trentham-Dietz,[1,3] Barbara E.K. Klein,[2] Ronald Klein,[2] Karen J. Cruickshanks,[1,2] Kristine E. Lee,[2] and John M. Hampton[3]

Departments of [1]Population Health Sciences and [2]Ophthalmology and Visual Sciences, University of Wisconsin, and [3]University of Wisconsin Paul P. Carbone Comprehensive Cancer Center, Madison, Wisconsin

Abstract

Previous studies have suggested that physical activity may lower lung cancer risk. The association of physical activity with reduced chronic inflammation provides a potential mechanism, yet few studies have directly related inflammatory markers to cancer incidence. The relation among physical activity, inflammation, and lung cancer risk was evaluated in a prospective cohort of 4,831 subjects, 43 to 86 years of age, in Beaver Dam, Wisconsin. A total physical activity index was created by summing up kilocalories per week from sweat-inducing physical activities, city blocks walked, and flights of stairs climbed. Two inflammatory markers, WBC count and serum albumin, were measured at the baseline examination. During an average of 12.8 years of follow-up, 134 incident cases of lung cancer were diagnosed. After multivariable adjustment, participants in the highest tertile of total physical activity index had a 45% reduction in lung cancer risk compared with those in the lowest tertile (hazard ratio, 0.55; 95% confidence interval, 0.35-0.86). Participants with WBC counts in the upper tertile ($\geq 8 \times 10^3/\mu L$) were 2.81 (95% confidence interval, 1.58-5.01) times as likely to develop lung cancer as those with counts in the lowest tertile ($<6.4 \times 10^3/\mu L$). Serum albumin was not related to lung cancer risk. There was no evidence that inflammation mediated the association between physical activity and lung cancer risk, as the physical activity risk estimates were essentially unchanged after adjustment for WBC count. Although the potential for residual confounding by smoking could not be eliminated, these data suggest that physical activity and WBC count are independent risk factors for lung cancer. (Cancer Epidemiol Biomarkers Prev 2008;17(10):2714–22)

Introduction

Lung cancer is the leading cause of cancer death among men and women in the United States (1). Strategies to reduce lung cancer risk besides smoking prevention and cessation are poorly understood. A number of epidemiologic studies have suggested that physical activity may reduce the risk of lung cancer (2-13), with a recent meta-analysis concluding that higher levels of leisure-time physical activity protect against lung cancer (14). In 2002, however, the IARC concluded that the evidence for an association between physical activity and lung cancer remained inconclusive, and two large studies recently found no consistent association between physical activity and lung cancer risk (15, 16).

The value of molecular biomarkers in discerning the relation between physical activity and cancer has recently been recognized (17, 18). The incorporation of biomarkers can be particularly helpful in clarifying inconclusive epidemiologic evidence and investigating potential mechanisms by which physical activity exerts its effects (17). A number of potential mechanisms through which physical activity may offer protection from lung cancer have been proposed. Physical activity and physical fitness are consistently observed to be associated with reduced chronic inflammation, reflected in lower levels of the inflammatory markers serum C-reactive protein, fibrinogen and WBC count, and increased levels of serum albumin (a negative acute-phase protein; refs. 19-23). Chronic inflammation has been hypothesized to be a risk factor for a wide range of cancers (24-26). Thus, physical activity could reduce lung cancer risk by reducing chronic inflammation. Yet few studies have directly evaluated markers of inflammation in relation to lung cancer incidence (27-30).

We investigated the relation between self-reported physical activity and lung cancer in an established cohort of older adults. Additionally, we measured two inflammatory markers, WBC count and serum albumin, in baseline blood samples to evaluate whether inflammation mediates the relation between physical activity and lung cancer.

Materials and Methods

Study Population. Descriptions of the population and the methods used to identify the population have been previously published (31-33). Briefly, a private census of the population living in Beaver Dam, Wisconsin, was done by the University of Wisconsin Extension-Survey Research Laboratory between September 15, 1987, and May 4, 1988. Eligibility requirements for entry into the study included living in the city or township of Beaver

Received 1/15/08; revised 6/20/08; accepted 7/25/08.

Grant support: Faculty startup funds from the University of Wisconsin School of Medicine and Public Health, NIH grants U10 EY006594 and R01 AG11099, and grant HS06941 by the Agency for Healthcare Research and Quality.

Requests for reprints: Amy Trentham-Dietz, University of Wisconsin, 610 Walnut Street, WARF Room 701, Madison WI 53726. Phone: 608-263-1946; Fax: 608-265-5330; E-mail: trentham@wisc.edu.

doi:10.1158/1055-9965.EPI-08-0042

DOI:10.1158/1055-9965.EPI-08-0042

Dam and being 43 to 84 y of age at the time of the census. A total of 5,925 eligible individuals were identified who met the criteria.

Of the 5,925 eligible individuals, 4,926 (83.1%) participated in the study examination, including 2,166 men and 2,760 women. The reasons for nonparticipation included 225 deaths (3.8%) before the examination, moving out of the area by 91 people (1.5%), failure to locate 23 people (0.4%), and refusal to participate by 391 (6.6%). Eligible participants who completed telephone interviews but were not examined (n = 269; 4.5%) were not included in this analysis, so that data were available for 4,926 participants who consented to examinations.

Case Identification. Incident cases of lung cancer (International Classification of Diseases for Oncology codes C34.0-34.9; ref. 34) diagnosed in study participants through July 2004 were identified through linkages with the Wisconsin Cancer Reporting System (the statewide mandatory tumor registry), Wisconsin death certificates, and the National Death Index. Deaths due to lung cancer identified through death records that were not also identified by the tumor registry (n = 7) were assigned a date of diagnosis equal to the average length of time from diagnosis to death for lung cancer cases in the Wisconsin tumor registry subtracted from their date of death (13 mo).

Data Collection. All participants provided signed informed consent at the time of the examination. Study questionnaires elicited information on comorbidities, reproductive and menstrual histories (for females), lifestyle factors, health history, medication histories, and demographics. Lifestyle factors on the questionnaires included physical activity, alcohol and caffeinated beverage consumption, smoking history, vitamin and mineral supplement use, and occupational history. Participants reported histories of diagnosis with major chronic medical conditions and surgical history. Collected demographic information included race/ethnicity and education, and participants were asked to report their marital status and income category.

To assess smoking history, subjects were asked if they had smoked more than 100 cigarettes in their lifetime, how many years they have smoked cigarettes, whether they smoke now, how long ago they stopped, and how many cigarettes they smoked per day (currently, or "usually" during smoking history for former smokers).

To assess physical activity, subjects were asked to report the number of city blocks walked per day (12 blocks = 1 mile), flights of stairs climbed per day, and the number of episodes of "regular activity long enough to work up a sweat" each week (35). A summary measure of total physical activity was created by summing the kilocalories (kcal) per week from blocks walked, flights of stairs climbed, and episodes of sweat-inducing activities. For 1 block walked per day and 1 flight of stairs climbed per day, we assigned 56 kcal/wk and 28 kcal/wk, respectively, as previously

Table 1. Selected participant characteristics at baseline according to physical activity levels

Characteristics at baseline	Episodes of sweat-inducing activities/wk (%)*		City blocks walked/d (%)*		Flights of stairs climbed/d (%)*	
	None (n = 3,215)	1 or more (n = 1,614)	None (n = 2,204)	1 or more (n = 2,610)	0-2 (n = 2,187)	3 or more (n = 2,639)
Age, y						
43-49	16	20	16	18	12	22
50-59	26	30	25	29	24	30
60-69	27	30	28	28	28	28
70-79	23	17	22	20	27	16
80-86	9	3	9	5	10	4
Sex						
Male	43	45	37	49	39	47
Female	57	55	63	51	61	53
Smoking status						
Never	45	45	47	43	46	44
Former	32	41	33	38	36	35
Current	23	14	21	19	18	21
Body mass index tertile (kg/m^2)						
1 (<26.2)	32	36	32	34	31	35
2 (26.2-30.3)	33	36	31	36	32	35
3 (>30.3)	35	29	36	30	36	30
Alcohol drinks/wk						
None	53	45	56	46	56	46
<5	20	28	20	25	21	24
≥5	26	27	24	29	23	29
Education, y						
<12	34	19	33	25	36	23
12	44	43	44	43	42	45
>12	22	38	23	32	22	32
Mean (SD) heart rate†	38.6 (5.9)	37.5 (5.8)	38.5 (6.0)	38.0 (5.8)	38.5 (6.0)	38.0 (5.8)
Mean (SD) WBC count (×10^3/μL)	7.5 (2.2)	7.1 (1.9)	7.5 (2.2)	7.3 (2.1)	7.6 (2.3)	7.2 (2.0)
Mean (SD) albumin (g/dL)	4.6 (0.4)	4.7 (0.3)	4.6 (0.4)	4.7 (0.4)	4.6 (0.4)	4.7 (0.4)

*Information regarding episodes of activity was missing for 2 participants, blocks walked was missing for 17 participants, and stairs climbed was missing for 5 participants.
†Thirty-second heart rate.

DOI:10.1158/1055-9965.EPI-08-0042

Table 2. HR and 95% CI of lung cancer according to physical activity levels and inflammatory markers

	No. cases	Person-years*	HR (95% CI)†	P_{trend}†	HR (95% CI)‡	P_{trend}‡
Episodes of sweat-inducing activities/wk						
0	105	36,753	1		1	
1-3	10	10,862	0.44 (0.23-0.85)		0.45 (0.23-0.87)	
≥4	19	9,611	0.75 (0.45-1.24)	0.08	0.76 (0.46-1.26)	0.09
City blocks walked/d						
0	73	25,117	1		1	
1-11	44	19,633	0.93 (0.63-1.37)		0.92 (0.62-1.35)	
≥12	17	12,292	0.53 (0.31-0.90)	0.03	0.52 (0.30-0.89)	0.02
Flights of stairs climbed/d						
0-1	44	17,715	1		1	
2-5	60	20,224	1.53 (1.02-2.29)		1.53 (1.02-2.29)	
>5	30	19,254	0.84 (0.52-1.36)	0.58	0.86 (0.53-1.40)	0.67
Total physical activity index (kcal/wk)§						
0-174	65	18,531	1		1	
175-874	38	19,120	0.72 (0.47-1.09)		0.72 (0.48-1.09)	
≥875	31	19,358	0.55 (0.35-0.86)	0.01	0.56 (0.35-0.87)	0.01
Heart rate (30 s)						
21-33	27	12,065	1		1	
34-42	70	33,925	0.93 (0.59-1.46)		0.95 (0.60-1.49)	
>42	37	11,235	1.30 (0.80-2.16)	0.27	1.25 (0.75-2.09)	0.35
WBC tertile ($\times 10^3/\mu L$)						
<6.4	16	19,605	1		—	
6.4-7.9	50	19,421	2.74 (1.53-4.90)		—	
≥8	68	18,019	2.81 (1.58-5.01)	0.001	—	
Albumin tertile (g/dL)						
<4.6	52	19,307	1		—	
4.6-4.8	51	20,321	1.02 (0.69-1.52)		—	
≥4.9	31	17,427	0.85 (0.54-1.34)	0.52	—	

*Total person-years for cases and noncases in category of activity.
†Models are adjusted for age, sex, pack-years of smoking, time since smoking cessation, body mass index, alcohol intake, and education.
‡Models are adjusted for all variables in †, plus WBC count.
§Kilocalories per week from city blocks walked, flights of stairs climbed, and sweat-inducing activities (see Materials and Methods).

used in the analyses of the Harvard Alumni Health Study (5, 6, 36). The duration and intensity of participation in sweat-inducing activities were not ascertained; a typical duration of 30 min at a multiple of resting metabolic rate of 7 was assumed (equivalent to jogging or tennis; ref. 37). Given a resting metabolic rate of 1 kcal/kg/h and the median subject weight of 76 kg, each sweat-inducing activity episode per week was assigned 266 kcal [= 7 × (1 kcal/kg/h) × (76 kg) × (0.5 h)].

Objective measures of comorbidity were collected in addition to self-reported chronic health conditions. Standardized procedures were used to measure height, weight, heart rate, vision, hearing, and blood pressure during the examination (31).

Laboratory Analysis. Casual venous blood specimens were obtained at the baseline examination for laboratory analysis. The collection, storage, and laboratory methods for the analysis of serum inflammatory markers have been previously described (38). Immediately after obtaining the baseline blood sample, WBC count was determined using the Coulter counter method, and serum albumin levels were determined by Technicon, Inc.

Statistical Analysis. Cox proportional hazards regression was used to estimate the hazard ratio (HR) and 95% confidence intervals (95% CI) of lung cancer associated with levels of physical activity and inflammatory markers. We tested proportionality assumptions and found no evidence of violation. Regression models were fitted according to the number of episodes of sweat-inducing activities, the number of blocks walked, the number of flights of stairs climbed, total physical activity index, heart rate, WBC count, and serum albumin level. With the exception of heart rate, the physical activity and inflammatory marker variables were categorized roughly by person-year tertiles, using round numbers as cutpoints. For sweat-inducing activities and city blocks walked per week, more than one third of person-years had zero activities. All models were adjusted for age (<50, 50-59, 60-69, 70-79, ≥80 y), sex, pack-years of smoking (none, tertiles), time since smoking cessation (never smoker, current smoker, quartiles), body mass index (kg/m^2, tertiles), alcohol intake (none, <5 drinks/wk, ≥5 drinks/wk), and education (<high school, high school degree, > high school). *P* values for trend were evaluated by including categorical variables in the models as continuous linear terms. Age and other covariates were assessed as effect modifiers of the association between physical activity and lung cancer by evaluating the change in the log-likelihood after including their cross-product terms in the regression models. In analyses stratified by smoking history, subjects were considered current smokers if they responded affirmatively to the questionnaire item "Do you smoke now?" and former smokers if they responded negatively but had smoked more than 100 cigarettes in their lifetime. Never and former smokers were combined in the stratified analysis because of insufficient numbers of each separately. Plots of cumulative lung cancer incidence according to the total physical activity index and WBC count were produced using the Kaplan-Meier method.

DOI:10.1158/1055-9965.EPI-08-0042

Least squared means and P values comparing WBC count and serum albumin according to tertiles of total physical activity index were calculated using multivariable ANOVA including covariates for smoking history. The mean levels of WBC count and serum albumin at baseline among participants who subsequently developed lung cancer were compared with levels corresponding to participants without lung cancer during the follow-up period using t tests. The values of albumin and WBC count were not transformed for the t tests because they were approximately normally distributed. P values using Wilcoxon nonparametric tests were essentially identical to those obtained using t tests, and are not shown.

Study participants reporting a personal history of lung cancer at the baseline examination ($n = 7$), or identified as a case of lung cancer within 12 mo of the baseline examination ($n = 6$), were excluded from the analysis. An additional 82 people who died within 12 mo of their baseline examination were also excluded from this analysis.

Results

During 62,062 person-years of follow-up (an average of 12.8 years per person), 134 cases of lung cancer were diagnosed among the 4,831 subjects without a personal history of lung cancer who survived at least 1 year after the baseline examination. Among cases, the mean time between baseline examination and diagnosis was 8.0 years (SD, 3.8; range, 1.2-16.3 years). According to

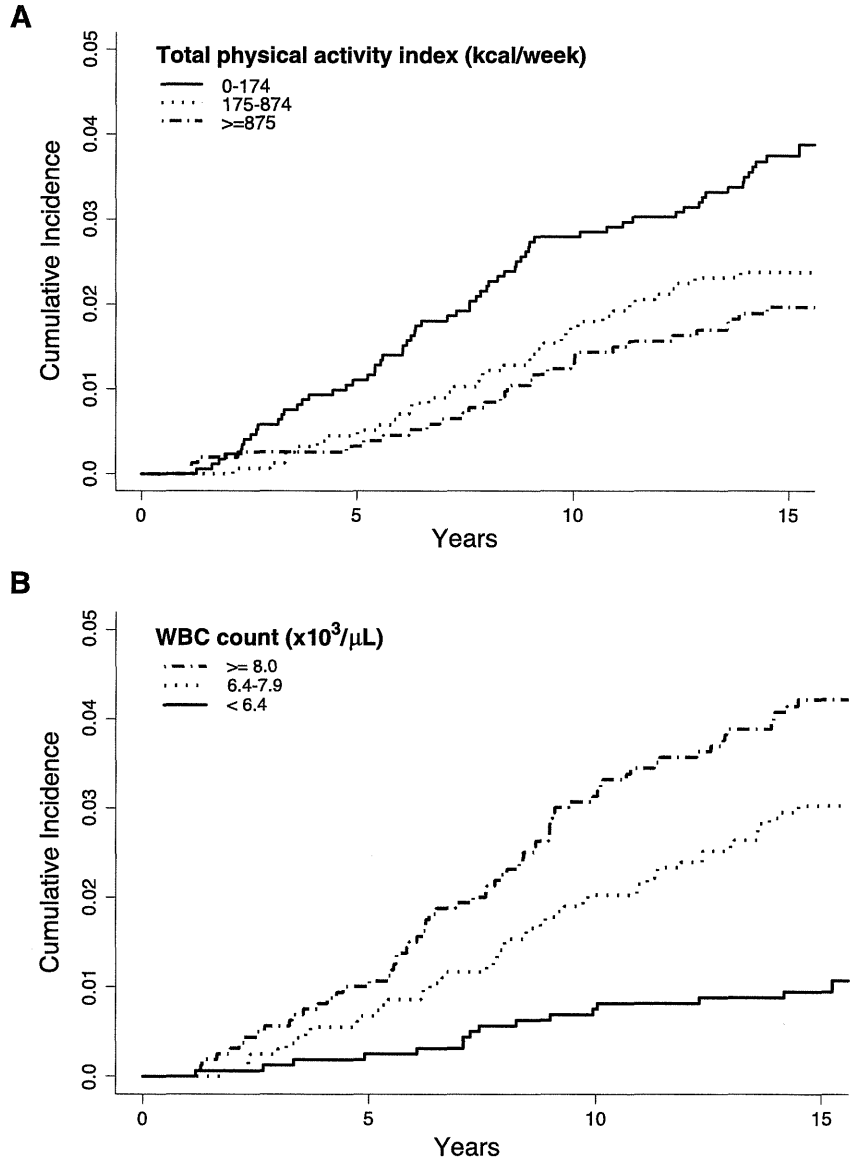


Figure 1. Lung cancer cumulative incidence according to total physical activity index (**A**) and WBC count (**B**). Note that lung cancer cases diagnosed within the first year following the baseline exam were excluded.

DOI:10.1158/1055-9965.EPI-08-0042

Table 3. HR and 95% CI of lung cancer according to physical activity by smoking status and gender

Total physical activity index (kcal/wk)*	No. cases	Person-years †	HR (95% CI) ‡	P_{trend} ‡
Current smokers				
0-174	36	4,052	1	
175-874	15	4,026	0.48 (0.26-0.91)	
≥875	12	3,107	0.49 (0.25-0.97)	0.02
Never/former smokers				
0-174	29	14,477	1	
175-874	23	15,081	0.97 (0.55-1.71)	
≥875	19	16,236	0.60 (0.33-1.11)	0.10
Females				
0-174	28	11,941	1	
175-874	17	10,737	1.02 (0.54-1.95)	
≥875	10	10,166	0.66 (0.30-1.44)	0.35
Males				
0-174	37	6,590	1	
175-874	21	8,383	0.56 (0.33-0.97)	
≥875	21	9,192	0.50 (0.29-0.87)	0.01

*Kilocalories per week from city blocks walked, flights of stairs climbed, and sweat-inducing activities (see Materials and Methods).
†Total person-years for cases and noncases in category of activity.
‡Models are adjusted for age, sex, pack-years of smoking, time since smoking cessation, body mass index, alcohol intake, and education.

tumor registry reports, 51% of the cases were non–small-cell type (23% adenocarcinoma, 14% squamous, 10% large cell, and 4% not otherwise specified), 12% were small-cell type, and 37% were unspecified-cell types. Of the cases, 23 (17%) were local, 27 (20%) were regional, 45 (34%) were distant, and 39 (29%) were unknown stage at diagnosis.

Physical activity variables are summarized according to other selected covariates in Table 1. In general, participants who were more active tended to be younger, have lower body mass, drink more alcohol, and report more years of education than less active participants. The distribution of participants according to smoking status within levels of physical activity depended upon the type of activity: current smokers were less likely to report vigorous activities that caused a sweat but more likely to climb stairs. Participants who were more active had lower heart rates and WBC counts than less active participants. After adjusting for smoking status, pack-years, and time since cessation, WBC counts declined in successive total physical activity index tertiles (7.6, 7.4, and 7.1 $\times$ $10^3/\mu L$, respectively; $P < 0.001$). No differences were observed in serum albumin according to physical activity levels.

Higher levels of physical activity at baseline were inversely associated with lung cancer incidence (Table 2; Fig. 1A). After multivariable adjustment for demographic and lifestyle factors (first column of HR), the risk of lung cancer was reduced by over 40% among participants reporting 12 or more city blocks walked per day (P_{trend} = 0.03) and those in the highest tertile of the total physical activity index (≥875 kcal/wk; P_{trend} = 0.01). There was a negative association between lung cancer risk and the weekly number of episodes of activity vigorous enough to cause a sweat, although a dose-response pattern was not observed (P_{trend} = 0.08). Flights of stairs climbed each day (P_{trend} = 0.58) and heart rate (P_{trend} = 0.27) were both not associated with lung cancer risk. Although power was limited to detect a difference, these associations between physical activity measures and lung cancer did not seem to differ strongly according to sex, age, body mass index, smoking status, or pack-years smoked. Reductions in lung cancer risk were observed with increasing total physical activity index scores in both current and never/former smokers, although the risk reduction was somewhat stronger and statistically significant only in current smokers (Table 3; $P_{interaction}$ = 0.99). Similarly, lung cancer risk appeared to decline with increasing total physical activity index scores among both men and women, although the risk reduction was stronger and statistically significant only in men (Table 3; $P_{interaction}$ = 0.55). The mean WBC count for lung cancer cases was significantly higher at baseline (mean, 8.2 $\times$ $10^3/\mu L$; SD, 2.2 $\times$ $10^3/\mu L$) than for participants who did not develop lung cancer (mean, 7.4 $\times$ $10^3/\mu L$; SD, 2.1 $\times$ $10^3/\mu L$; $P < 0.0001$). After multivariable adjustment, the HR for lung cancer was 2.8 times as high in participants with WBC counts ≥8 $\times$ $10^3/\mu L$ compared with those having counts <6.4 $\times$ $10^3/\mu L$ (Table 2; Fig. 1B). The mean levels of albumin at baseline among the lung cancer cases were essentially the same (mean, 4.6 g/dL; SD, 0.4 g/dL) as for noncases (mean, 4.7 g/dL; SD, 0.4 g/dL; P = 0.17), and no association was observed after multivariable adjustment.

The variables in Table 2 were similarly associated with lung cancer incidence and lung cancer mortality (data not shown), although for WBC count the relation was somewhat stronger for lung cancer mortality (HR, 3.75; 95% CI, 1.89-7.42 for tertile 3 versus tertile 1).

The results shown in Table 2 were negligibly affected by further adjustment for the presence of diabetes and emphysema at baseline (data not shown). Similarly, the further exclusion of 7 cases diagnosed between 12 and 24 months after the baseline examination had a negligible effect on the results. The relations among lung cancer risk, physical activity, and WBC count did not seem to be modified by time since the baseline examination. In analyses stratified by the median time between baseline exam and diagnosis (7.9 years), lung cancer risk was associated with physical activity and WBC count for both time frames (data not shown). There was limited power to examine these relations by histologic subtype. Compared with subjects in the lowest total physical activity index tertile, subjects in the highest tertile were 0.73 (95%

DOI:10.1158/1055-9965.EPI-08-0042

CI, 0.40-1.31) times as likely to develop any non–small cell lung cancer and 0.95 (95% CI, 0.41-2.21) times as likely to develop adenocarcinoma. Subjects in the highest tertile of WBC count were 3.04 (95% CI, 1.31-7.07) times more likely to develop non–small cell lung cancer and 2.42 (95% CI, 0.89-6.82) times more likely to develop adenocarcinoma than those in the lowest tertile. Too few cases were available to evaluate other specific cell types according to physical activity or WBC count.

To assess whether the inverse association between physical activity and lung cancer risk was mediated by inflammation, the regression models evaluating the physical activity/lung cancer association were additionally adjusted for WBC count at baseline (Table 2, second column of HR). This adjustment led to very minimal changes in the lung cancer HRs associated with the various measures of physical activity. Similarly, the lung cancer HRs associated with WBC count were not substantially changed after additionally adjusting for total physical activity index (HR, 2.76; 95% CI, 1.54-4.95 and HR, 2.76; 95% CI,1.55-4.91, for 6.4-7.9 $\times$ $10^3/\mu L$ and $\geq 8 \times 10^3/\mu L$ versus $<6.4 \times 10^3/\mu L$, respectively). Finally, WBC count did not seem to modify the relation between total physical activity index and lung cancer risk ($P_{interaction} = 0.86$).

Discussion

In this study, we found an inverse association between physical activity and lung cancer risk. We also found evidence for a positive association between lung cancer risk and WBC count, but not serum albumin. It has been hypothesized that physical activity may lower lung cancer risk by reducing chronic inflammation. We found no evidence, however, that the associations of physical activity and WBC count with lung cancer risk were mediated through the same biological pathway.

Clearly smoking is a strong causal factor of lung cancer in both men and women, with a population attributable risk of approximately 75% to 90% in the United States (39, 40). Smoking prevention and cessation are the primary prevention strategies needed to reduce lung cancer incidence. However, the elucidation of other risk factors would aid in lung cancer prevention, particularly in never and former smokers, in whom ~50% of all new lung cancers are diagnosed (41). This study adds additional evidence to the body of literature that suggests that physical activity is a protective factor against the development of lung cancer.

We observed an inverse association between physical activity and lung cancer at the upper end of the 10% to 40% range of risk reductions observed in the majority of past studies (14). Given the strong relation between smoking and lung cancer risk, residual confounding of the relation between lung cancer risk and both physical activity and WBC count remains a concern. In models adjusted for sex, body mass index, alcohol, and education, but not smoking, the relations between lung cancer and physical activity and WBC count were stronger (HR, 0.43 and HR, 5.05 for third tertile versus first tertile of total physical activity index and WBC count, respectively) than in models fully adjusted for smoking (HR, 0.55 and HR, 2.81, respectively). Thus, it is possible that better measurement of smoking (e.g., more accurate reporting, biomarkers of smoking history) would further attenuate our findings. However, we were able to adjust for a number of prospectively obtained self-reported smoking parameters, including smoking status, amount of smoking (pack-years), and time since smoking cessation. In analyses stratified by smoking status, physical activity seemed to be associated with reduced lung cancer risk among never and former smokers combined, although this did not reach statistical significance. Too few cases were observed among never smokers ($n = 16$) to examine this stratum separately. The relation between smoking and adenocarcinoma is weaker than for other cell types (42). In our data, adenocarcinoma was associated with WBC count but not total physical activity index score. Although this was based on only 31 events, it suggests additional caution in interpreting the physical activity/lung cancer association.

Exercise is associated with reduced systemic inflammation (particularly C-reactive protein) both between persons in cross-sectional studies and within persons after the initiation of training regimens (21). Inflammation has been proposed to promote carcinogenesis in a wide spectrum of cancers, including lung, through its effects on cell proliferation, survival, and migration (24-26). Inflammatory lung conditions, such as chronic bronchitis and asthma, have previously been linked with increased lung cancer risk (43). Furthermore, the use of aspirin and other nonsteroidal anti-inflammatory drugs has been associated with reduced lung cancer risk (44, 45).

We investigated the relation between two inflammatory markers and lung cancer. WBC count is a widely used nonspecific marker of systemic inflammation (26, 46, 47). We observed reduced WBC counts in participants who reported higher physical activity levels, consistent with previous findings (19, 23, 48). Notably, we found that this relation persisted after adjustment for self-reported smoking history. Three studies have reported positive associations between WBC count and lung cancer incidence or mortality after adjustment for smoking (30, 46, 47). Similar to our study, Shankar et al. (46) reported increased lung cancer mortality among subjects in the upper quartile of WBC count compared with those in the lowest quartile (risk ratio, 2.58; 95% CI, 0.72-9.26 for quartile 4 versus quartile 1). The results from our study (incidence HR, 2.81; 95% CI, 1.58-5.01, and mortality HR, 3.75; 95% CI, 1.89-7.42) and Shankar et al. (46) provide greater risk estimates than those for quartile 4 versus quartile 1 of WBC count in Erlinger et al. (ref. 47; mortality HR, 1.79; 95% CI, 0.88-3.62) and the recently reported results of the Women's Health Initiative (ref. 30; incidence HR, 1.63; 95% CI, 1.35-1.97). The Women's Health Initiative observed little difference between lung cancer incidence and mortality HRs in relation to WBC count.

Serum albumin is a negative acute phase protein: its concentration in the blood is reduced in response to inflammation (49, 50). At least one study has reported an approximate 25% reduction in cancer mortality among middle-aged men with a 1 SD increase in serum albumin (51). We observed little difference in serum albumin among participants according to physical activity level, and no association between serum albumin and lung cancer risk.

DOI:10.1158/1055-9965.EPI-08-0042

To investigate the hypothesis that physical activity lowers lung cancer risk by decreasing systemic inflammation, we further adjusted the regression model of physical activity and lung cancer risk for WBC count. In an adequately adjusted model, one would expect the association between physical activity and lung cancer risk to be attenuated if the relation was mediated at least in part by inflammation (represented by WBC count; ref. 52). However, we found that the associations between lung cancer risk and both physical activity and WBC count were practically unchanged after simultaneous adjustment. Thus, the effect of physical activity on lung cancer risk does not seem to be mediated by inflammation, as represented by WBC count. Importantly, WBC count is only one marker of inflammation; it remains possible that other measures of inflammation may be more relevant to the relation of physical activity and lung cancer.

Physical activity has been proposed to lower lung cancer risk by a variety of other mechanisms. Physical activity might reduce the concentration of carcinogenic agents in the airways, the duration of agent-airway interaction, and particle deposition through increased ventilation and perfusion (53). Physical activity also reduces insulin-like growth factor levels that stimulate cell proliferation (54). Furthermore, physical activity may enhance immune function or endogenous antioxidant defenses (17, 55, 56).

A number of limitations must be considered in the interpretation of this study. We used a simple assessment of physical activity. Although an increased heart rate is an objective measure associated with lack of physical activity (57, 58), heart rate is also modified by general health, stress, and other psychosocial factors. Questions regarding the number of blocks walked per week and flights of stairs climbed per day have previously been used in combination with data on recreational physical activity to measure the relation between physical activity and cancer risk in the Harvard Alumni Health Study (5, 6, 59). We did not collect data on specific participation in recreational physical activities, but rather episodes of sweat-inducing activities. A moderate correlation (r = 0.54-0.62) has been reported between episodes of sweat-inducing activities and the Harvard Alumni Activity Survey scores (60, 61), including one study in a population of older women (62). The association between sweat-inducing activities and physical fitness measured on a cycle ergometer, however, has been reported to be stronger in men (r = 0.46) than in women (r = 0.26; ref. 60). Our summary physical activity measure that combined blocks walked, stairs climbed, and sweat-inducing activities was more strongly related to lung cancer risk among men than in women (Table 3), although the test for effect modification did not reach statistical significance ($P_{interaction}$ = 0.46).

The limited scope of our physical activity assessment failed to capture variation in the intensity and duration of sweat-inducing activities. To create our total physical activity index, we assumed a typical duration of 30 minutes for sweat-inducing activities, with an intensity level equivalent to jogging (multiple of resting metabolic rate = 7). The results did not seem sensitive to variation in these assumptions: assuming a multiple of resting metabolic rate of 5 for 30 minutes or a multiple of resting metabolic rate of 9 for 1 hour for sweat-inducing activities, both resulted in a HR of 0.55 for the third tertile of total physical activity index compared with the first tertile.

Notably, our physical activity assessment also failed to capture past history of physical activity. Our failure to capture variation in duration, intensity, and past history of activity would be expected to attenuate the reductions in risk observed in our study. Much more sophisticated assessments of physical activity have been developed since the initiation of our study. Further studies are necessary, in particular, to evaluate lung cancer risk in relation to cumulative lifetime physical activity and to discriminate the effects of physical activity during different time periods in life.

Other unmeasured aspects of a healthy lifestyle may confound the relation between physical activity and lung cancer. A diet high in fruits and vegetables has been associated with reduced lung cancer risk (63). Unfortunately, we had limited information on diet and were unable to control for this in our analysis.

The strengths of this study included a population-based cohort of both sexes with excellent follow-up, the prospective assessment of physical activity and inflammatory markers, and the ability to control for a number of prospectively obtained smoking parameters. It is possible that lower levels of physical activity among future cases might be expected at the baseline exam due to symptoms related to undiagnosed lung cancer, such as pain or fatigue. To reduce the potential for this bias, we excluded all lung cancer cases who were diagnosed within 12 months of the baseline examination (n = 13). Other diseases, particularly of the lung, may also influence physical activity, inflammation, and lung cancer risk. However, we observed little change in the relations among lung cancer risk, physical activity, and WBC count after adjusting for self-reported emphysema and diabetes.

Lung cancer is both the most common cancer diagnosis in the world and the most common cause of death from cancer (64). The global burden of smoking-related disease is overwhelming, with over 1.3 million new cases of lung cancer and approximately 1.2 million deaths in 2002 (64). Smoking prevention and cessation are imperative in reducing the mortality associated with this disease. Continued study of physical activity in relation to lung cancer risk, particularly among never smokers, may further our understanding of this disease and reveal additional strategies for reducing its burden.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

We thank Dr. Dennis Fryback, Scot Moss, Michael Knudtson, Dr. Lisa Colbert, Laura Stephenson, and the staff of the Wisconsin Cancer Reporting System; and Hazel Nichols, Andy Bersch, Moneen Meuer, and the participants of the Beaver Dam Studies for their invaluable contributions.

DOI:10.1158/1055-9965.EPI-08-0042

References

1. Ries LAG, Melbert D, Krapcho M, et al. SEER cancer statistics review, 1975–2004. Bethesda (MD): National Cancer Institute, http://seer.cancer.gov/csr/1975_2004/, based on November 2006 SEER data submission, posted to the SEER website, 2007.
2. Albanes D, Blair A, Taylor PR. Physical activity and risk of cancer in the NHANES I population. Am J Public Health 1989;79:744–50.
3. Brownson RC, Chang JC, Davis JR, Smith CA. Physical activity on the job and cancer in Missouri. Am J Public Health 1991;81:639–42.
4. Kubik A, Zatloukal P, Boyle P, et al. A case-control study of lung cancer among Czech women. Lung Cancer 2001;31:111–22.
5. Lee IM, Paffenbarger RS, Jr. Physical activity and its relation to cancer risk: a prospective study of college alumni. Med Sci Sports Exerc 1994;26:831–7.
6. Lee IM, Sesso HD, Paffenbarger RS, Jr. Physical activity and risk of lung cancer. Int J Epidemiol 1999;28:620–5.
7. Mao Y, Pan S, Wen SW, Johnson KC. Physical activity and the risk of lung cancer in Canada. Am J Epidemiol 2003;158:564–75.
8. Olson JE, Yang P, Schmitz K, Vierkant RA, Cerhan JR, Sellers TA. Differential association of body mass index and fat distribution with three major histologic types of lung cancer: evidence from a cohort of older women. Am J Epidemiol 2002;156:606–15.
9. Sellers TA, Potter JD, Folsom AR. Association of incident lung cancer with family history of female reproductive cancers: the Iowa Women's Health Study. Genet Epidemiol 1991;8:199–208.
10. Thune I, Lund E. The influence of physical activity on lung-cancer risk: a prospective study of 81,516 men and women. Int J Cancer 1997;70:57–62.
11. Alfano CM, Klesges RC, Murray DM, et al. Physical activity in relation to all-site and lung cancer incidence and mortality in current and former smokers. Cancer Epidemiol Biomarkers Prev 2004;13:2233–41.
12. Sinner P, Folsom AR, Harnack L, Eberly LE, Schmitz KH. The association of physical activity with lung cancer incidence in a cohort of older women: the Iowa Women's Health Study. Cancer Epidemiol Biomarkers Prev 2006;15:2359–63.
13. Kubik A, Zatloukal P, Tomasek L, Pauk N, Petruzelka L, Plesko I. Lung cancer risk among nonsmoking women in relation to diet and physical activity. Neoplasma 2004;51:136–43.
14. Tardon A, Lee WJ, Delgado-Rodriguez M, et al. Leisure-time physical activity and lung cancer: a meta-analysis. Cancer Causes Control 2005;16:389–97.
15. Bak H, Christensen J, Thomsen BL, et al. Physical activity and risk for lung cancer in a Danish cohort. Int J Cancer 2005;116:439–44.
16. Steindorf K, Friedenreich C, Linseisen J, et al. Physical activity and lung cancer risk in the European Prospective Investigation into Cancer and Nutrition Cohort. Int J Cancer 2006;119:2389–97.
17. Rundle A. Molecular epidemiology of physical activity and cancer. Cancer Epidemiol Biomarkers Prev 2005;14:227–36.
18. Campbell KL, McTiernan A. Exercise and biomarkers for cancer prevention studies. J Nutr 2007;137:161–9S.
19. Ford ES. Does exercise reduce inflammation? Physical activity and C-reactive protein among U.S. adults. Epidemiology 2002;13:561–8.
20. Bruunsgaard H. Physical activity and modulation of systemic low-level inflammation. J Leukoc Biol 2005;78:819–35.
21. Kasapis C, Thompson PD. The effects of physical activity on serum C-reactive protein and inflammatory markers: a systematic review. J Am Coll Cardiol 2005;45:1563–9.
22. Hamer M. The relative influences of fitness and fatness on inflammatory factors. Prev Med 2007;44:3–11.
23. Pitsavos C, Chrysohoou C, Panagiotakos DB, et al. Association of leisure-time physical activity on inflammation markers (C-reactive protein, white cell blood count, serum amyloid A, and fibrinogen) in healthy subjects (from the ATTICA study). Am J Cardiol 2003;91:368–70.
24. O'Byrne KJ, Dalgleish AG. Chronic immune activation and inflammation as the cause of malignancy. Br J Cancer 2001;85:473–83.
25. Coussens LM, Werb Z. Inflammation and cancer. Nature 2002;420:860–7.
26. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet 2001;357:539–45.
27. Il'yasova D, Colbert LH, Harris TB, et al. Circulating levels of inflammatory markers and cancer risk in the health aging and body composition cohort. Cancer Epidemiol Biomarkers Prev 2005;14:2413–8.
28. Siemes C, Visser LE, Coebergh JW, et al. C-reactive protein levels, variation in the C-reactive protein gene, and cancer risk: the Rotterdam Study. J Clin Oncol 2006;24:5216–22.
29. Suzuki K, Ito Y, Wakai K, et al. Serum heat shock protein 70 levels and lung cancer risk: a case-control study nested in a large cohort study. Cancer Epidemiol Biomarkers Prev 2006;15:1733–7.
30. Margolis KL, Rodabough RJ, Thomson CA, Lopez AM, McTiernan A. Prospective study of leukocyte count as a predictor of incident breast, colorectal, endometrial, and lung cancer and mortality in postmenopausal women. Arch Intern Med 2007;167:1837–44.
31. Klein R, Klein BE, Linton KL, De Mets DL. The Beaver Dam Eye Study: visual acuity. Ophthalmology 1991;98:1310–5.
32. Klein R, Klein BE, Lee KE. Changes in visual acuity in a population. The Beaver Dam Eye Study. Ophthalmology 1996;103:1169–78.
33. Klein R, Klein BE, Lee KE, Cruickshanks KJ, Chappell RJ. Changes in visual acuity in a population over a 10-year period: the Beaver Dam Eye Study. Ophthalmology 2001;108:1757–66.
34. Fritz A, Percy C, Jack A, et al. International classification of diseases for oncology, 3rd ed. Geneva: WHO; 2000.
35. Knudtson MD, Klein R, Klein BE. Physical activity and the 15-year cumulative incidence of age-related macular degeneration: the Beaver Dam Eye Study. Br J Ophthalmol 2006;90:1461–3.
36. Paffenbarger RS, Jr., Wing AL, Hyde RT. Physical activity as an index of heart attack risk in college alumni. Am J Epidemiol 1978;108:161–75.
37. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exer 2000;32:S498–516.
38. Klein R, Klein BE, Knudtson MD, Wong TY, Tsai MY. Are inflammatory factors related to retinal vessel caliber? The Beaver Dam Eye Study. Arch Ophthalmol 2006;124:87–94.
39. U.S. Department of Health and Human Services. Reducing the health consequences of smoking: 25 years of progress. A report of the Surgeon General. Rockville (MD): U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. DHHS Publication No. (CDC) 89-8411, 1989.
40. Shopland DR. Tobacco use and its contribution to early cancer mortality with a special emphasis on cigarette smoking. Environ Health Perspect 1995;103 Suppl 8:131–42.
41. Tong L, Spitz MR, Fueger JJ, Amos CA. Lung carcinoma in former smokers. Cancer 1996;78:1004–10.
42. Sun S, Schiller JH, Gazdar AF. Lung cancer in never smokers-a different disease. Nat Rev Cancer 2007;7:778–90.
43. Mayne ST, Buenconsejo J, Janerich DT. Previous lung disease and risk of lung cancer among men and women nonsmokers. Am J Epidemiol 1999;149:13–20.
44. Schreinemachers DM, Everson RB. Aspirin use and lung, colon, and breast cancer incidence in a prospective study. Epidemiology 1994;5:138–46.
45. Smith CJ, Perfetti TA, King JA. Perspectives on pulmonary inflammation and lung cancer risk in cigarette smokers. Inhal Toxicol 2006;18:667–77.
46. Shankar A, Wang JJ, Rochtchina E, Yu MC, Kefford R, Mitchell P. Association between circulating white blood cell count and cancer mortality: a population-based cohort study. Arch Intern Med 2006;166:188–94.
47. Erlinger TP, Muntner P, Helzlsouer KJ. WBC count and the risk of cancer mortality in a national sample of U.S. adults: results from the Second National Health and Nutrition Examination Survey mortality study. Cancer Epidemiol Biomarkers Prev 2004;13:1052–6.
48. Church TS, Finley CE, Earnest CP, Kampert JB, Gibbons LW, Blair SN. Relative associations of fitness and fatness to fibrinogen, white blood cell count, uric acid and metabolic syndrome. Int J Obes Relat Metab Disord 2002;26:805–13.
49. Rothschild MA, Oratz M, Schreiber SS. Serum albumin. Hepatology 1988;8:385–401.
50. Don BR, Kaysen G. Serum albumin: relationship to inflammation and nutrition. Semin Dial 2004;17:432–7.
51. Phillips A, Shaper AG, Whincup PH. Association between serum albumin and mortality from cardiovascular disease, cancer, and other causes. Lancet 1989;2:1434–6.
52. Szklo M, Nieto FJ. Epidemiology: beyond the basics. Gaithersburg (MD): Aspen Publishers, Inc.; 1999.
53. IARC. IARC handbooks on cancer prevention, Vol. 6: Weight control and physical activity. Lyon (France): IARC Press; 2002.
54. Yu H, Rohan T. Role of the insulin-like growth factor family in cancer development and progression. J Natl Cancer Inst 2000;92:1472–89.
55. McTiernan A, Ulrich C, Slate S, Potter J. Physical activity and cancer

DOI:10.1158/1055-9965.EPI-08-0042

etiology: associations and mechanisms. Cancer Causes Control 1998; 9:487–509.
56. Rundle AG, Orjuela M, Mooney L, et al. Preliminary studies on the effect of moderate physical activity on blood levels of glutathione. Biomarkers 2005;10:390–400.
57. Benetos A, Rudnichi A, Thomas F, Safar M, Guize L. Influence of heart rate on mortality in a French population: role of age, gender, and blood pressure. Hypertension 1999;33:44–52.
58. Wannamethee G, Shaper AG, Macfarlane PW. Heart rate, physical activity, and mortality from cancer and other noncardiovascular diseases. Am J Epidemiol 1993;137:735–48.
59. Lee IM, Paffenbarger RS, Jr., Hsieh CC. Physical activity and risk of prostatic cancer among college alumni. Am J Epidemiol 1992;135:169–79.
60. Siconolfi SF, Lasater TM, Snow RC, Carleton RA. Self-reported physical activity compared with maximal oxygen uptake. Am J Epidemiol 1985;122:101–5.
61. Washburn RA, Adams LL, Haile GT. Physical activity assessment for epidemiologic research: the utility of two simplified approaches. Prev Med 1987;16:636–46.
62. LaPorte RE, Black-Sandler R, Cauley JA, Link M, Bayles C, Marks B. The assessment of physical activity in older women: analysis of the interrelationship and reliability of activity monitoring, activity surveys, and caloric intake. J Gerontol 1983;38:394–7.
63. World Cancer Research Fund. Food, nutrition and the prevention of cancer: a global perspective. Washington (DC): American Institute for Cancer Research; 1997. p. 130–47.
64. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74–108.