Time to Diagnosis and Treatment of Breast Cancer: Results From the National Breast and Cervical Cancer Early Detection Program, 1991–1995

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A B S T R A C T

Objectives. This study examined times to diagnosis and treatment for medically underserved women screened for breast cancer.

Methods. Intervals from first positive screening test to diagnosis to initiation of treatment were determined for 1659 women 40 years and older diagnosed with breast cancer.

Results. Women with abnormal mammograms had shorter diagnostic intervals than women with abnormal clinical breast examinations and normal mammograms. Women with self-reported breast symptoms had shorter diagnostic intervals than asymptomatic women. Diagnostic intervals were less than 60 days in 78% of cases. Treatment intervals were generally 2 weeks or less.

Conclusions. Most women diagnosed with breast cancer were followed up in a timely manner after screening. Further investigation is needed to identify and then address factors associated with longer diagnostic and treatment intervals to maximize the benefits of early detection. (*Am J Public Health*. 2000;90:130–134)

Since early diagnosis and treatment are associated with decreased breast cancer mortality, it is important to minimize the times from detection to diagnosis to treatment. The interval between self-discovery of breast symptoms and medical evaluation, the "patient delay," has been studied extensively.[1–5] The interval between initial medical consultation or screening and diagnosis or initiation of therapy—the"system delay"—has been investigated less, especially among asymptomatic women. Many symptomatic breast cancer patients experience long delays in obtaining diagnosis and treatment,[6–8] perhaps negatively affecting their prognosis.[7,8] Only 1 study has included screen-detected cancers, but it provided no survival data.[9]

This study explored the time required to diagnose and begin treating breast cancers that are screen-detected through the National Breast and Cervical Cancer Early Detection Program (NBCCEDP), which is administered by the Centers for Disease Control and Prevention (CDC). NBCCEDP provides breast and cervical cancer screening and diagnostic services to medically underserved women.[10] To realize the benefits of early detection, timely follow-up and treatment must occur.[11]

Methods

NBCCEDP has been described elsewhere.[10,12] Briefly, the CDC implemented cooperative agreements with state and territorial health agencies and American Indian/Alaskan Native tribal organizations to provide screening, referral, and follow-up services for underserved women. The program provides annual clinical breast examinations (CBEs) for all women and annual mammograms for women 40 years and older, along with diagnostic services. Programs contract with a broad range of providers, including health departments, community and migrant health centers, radiology facilities, private physicians, and community organizations, to coordinate and deliver services. Because the law prohibits federal payment for treatment, programs must find financial or in-kind support so that women diagnosed with cancer can receive timely and appropriate treatment. The CDC estimates that programs that have been in existence for several years reach about 10% to 15% of eligible women.

The CDC and its state partners developed a set of standardized data items to monitor screening, diagnostic, and follow-up activities. Women self-report demographic characteristics, mammography history, and breast symptoms. Providers report the results of mammograms and CBEs, the performance of diagnostic procedures, diagnostic results, and when treatment is initiated. Programs report data electronically to the CDC biennially. Thirty-five states and 6 tribal programs reported data during our study period. Each woman's zip code or county of residence and a US census data file were used to categorize residence as urban (within a standard metropolitan statistical area) or rural.

Most of the mammography offered through the program is for screening, but diagnostic mammography is also provided: eligible women may self-refer on the basis of symptoms or concerns, and women whose customary providers detect a breast abnormality may be referred for diagnostic evaluation. Approximately 20% of program mammographies may be diagnostic (performed after an abnormal CBE or self-reported symptoms).[12] We considered 3 time intervals: the diagnostic interval—the time between the date of the first examination (CBE or mammogram) that found an abnormality and the date of the pathologic diagnosis of cancer; the treatment interval—the time between the date of diagno-

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TABLE 1—Distribution of Times to Breast Cancer Diagnosis and Initiation of Treatment According to Screening Test Outcome: National Breast and Cervical Cancer Early Detection Program, 1991–1995

Clinical Breast Examination	Mammogram[a]	n	Diagnostic Interval: Time From First Abnormal Screening[b] to Diagnosis (Days)		Treatment Interval: Time From Diagnosis to Treatment Initiation (Days)		Total Interval: Time From First Abnormal Screening[b] to Treatment Initiation (Days)	
			Median (Range)	% > 60, d	Median (Range)	% > 30, d	Median (Range)	% > 90, d
All	All	1659	32 (0–759)	21.7	10 (0–791)	21.8	48 (0–845)	22.9
Abnormal	Abnormal	714	29 (0–759)	17.0	10 (0–641)	21.6	43 (0–827)	19.5
Abnormal	Normal	70	46 (0–574)	40.0	2 (0–111)	17.1	65 (6–574)	37.1
Normal	Abnormal	648	34 (0–450)	24.7	9 (0–791)	21.1	51 (1–845)	25.3
Not done/unknown	Abnormal	227	29 (0–398)	22.5	13 (0–202)	25.6	50 (1–511)	22.5
P			<.0001	<.001	.05	.40	.0003	.002

Note. *P* values for differences between medians within each set are based on the Kruskal-Wallis test. *P* values for differences between percentages over specified number of days within each set are based on the χ^2 test

[a]Standard reporting categories from the Breast Imaging and Reporting Data System.[13] Normal = negative, benign, or probably benign. Abnormal = suspicious abnormality, highly suggestive of malignancy, or assessment is incomplete.

[b]Abnormal finding in mammogram or clinical breast examination.

sis and the date the treatment plan was started; and the total interval—the time between the date of the first abnormal screening result and the date the treatment started.

Between July 1, 1991, and September 30, 1995, 325 035 examination cycles initiated by CBEs or mammograms were performed on 250 957 women 40 years or older. Of these cycles, 1907 resulted in a diagnosis of breast cancer. We excluded 61 women who refused treatment or were lost to follow-up and 58 others who had no record of an abnormal screening test. Also excluded were 118 women whose dates of diagnosis or initiation of treatment were not reported or predated the first abnormal examination. Finally, for 11 women with 2 breast cancers diagnosed through the program, we used the first. Thus, 1659 women with breast cancer diagnoses formed the basis for analysis.

The diagnostic, treatment, and total interval distributions were highly skewed because of a few extremely long intervals. Therefore, we compared medians rather than means to give a more accurate picture of the true distributions, using the Kruskal-Wallis test to assess statistical significance.[14] We also determined the percentages of women with diagnostic intervals longer than 60 days, treatment intervals longer than 30 days, and total intervals longer than 90 days, using the χ^2 test for significance. Although there is no consensus on reasonable lengths for these intervals, total intervals of up to 90 days are unlikely to adversely affect survival.[9]

TABLE 2—Cumulative Distribution of Time Intervals to Diagnosis of Breast Cancer and Initiation of Treatment: National Breast and Cervical Cancer Early Detection Program, 1991–1995

Interval, d	Women Diagnosed With Breast Cancer[a]: Diagnosis After First Abnormal Screen Within Interval Shown,[b] %	Treatment Initiated After Diagnosis Within Interval Shown, %	Treatment Initiated After Abnormal Screen Within Interval Shown,[b] %
5	6.0	41.9	1.3
10	14.0	51.7	4.3
15	24.2	59.4	8.4
20	32.2	66.0	13.0
30	48.9	78.2	26.4
40	62.0	84.6	40.2
50	71.4	88.1	53.1
60	78.3	90.7	61.0
80	85.3	93.1	72.8
100	89.6	95.1	80.3
120	91.9	96.2	85.2
140	93.9	96.7	88.7
160	94.8	97.0	90.2
180	95.5	97.2	91.3
200	96.1	97.4	92.5

[a]n = 1659.

[b]Abnormal finding in mammogram or clinical breast examination.

Results

Among women diagnosed with breast cancer after an abnormal mammogram, those with normal CBEs had a median diagnostic interval 5 days longer than those with abnormal or unknown CBE results (Table 1). Women with normal mammograms and abnormal CBEs had a median diagnostic interval 12 to 17 days longer than those with abnormal mammograms. Median treatment intervals were within 2 weeks, regardless of mammogram or CBE result.

Among women diagnosed with breast cancer, the cancer was diagnosed within 15 days of the first abnormal test for nearly one fourth of the women, within 30 days for nearly half, and within 60 days for more than three fourths (Table 2). Treatment intervals were substantially shorter than diagnostic intervals: nearly 80% of the women began treatment within 30 days after diagnosis.

Women 70 years or older had shorter treatment intervals than younger women (Table 3). White women had shorter diagnostic and treatment intervals than women of other racial or ethnic groups. Black and Hispanic women had the longest diagnostic intervals, and other/unknown and Asian women had the longest treatment intervals. Total intervals were shorter for rural than for urban women. Diagnostic intervals were shorter for symptomatic than for asymptomatic women. Women with the most ominous

TABLE 3—Distribution of Times to Breast Cancer Diagnosis and Initiation of Treatment According to Demographics, Symptoms, and Mammography Results: National Breast and Cervical Cancer Early Detection Program, 1991–1995

		Diagnostic Interval: Time From First Abnormal Screening[a] to Diagnosis, d		Treatment Interval: Time From Diagnosis to Treatment Initiation, d		Total Interval: Time From First Abnormal Screening[a] to Treatment Initiation, d	
	n	Median	% > 60, d	Median	% > 30, d	Median	% > 90, d
Age, y							
40–49	442	30	20.1	10	22.2	48	23.3
50–69	979	32	22.9	11	22.6	48	24.0
70+	238	34	19.8	6	17.7	46	17.7
P		.47	.37	.035	.25	.25	.11
Race/ethnicity							
White	975	29	17.7	8	19.9	43	18.4
Black	255	36	25.9	15	29.0	60	30.6
Hispanic	270	38	28.2	8	20.4	52	28.2
Asian	45	35	24.4	18	24.4	57	26.7
American Indian/Alaskan Native	97	33	30.9	14	22.7	55	32.0
Other/Unknown	17	29	23.5	21	29.4	50	23.5
P		<.0001	<.001	.004	.050	<.0001	< .001
County of residence							
Rural	532	28	21.8	8	17.5	44	21.1
Urban	1072	34	21.9	10	23.9	50	23.7
Unknown	55	22	16.4	16	21.8	43	25.5
P		.0002	.62	.05	.014	.002	.45
Breast symptoms							
Yes	516	29	19.0	8	21.7	44	21.3
No	826	35	23.5	10	21.9	51	23.2
Unknown	317	29	21.5	11	21.5	44	24.6
P		.0002	.15	.64	.99	.013	.52
Mammography result[b]							
Neg, Ben	34	47	41.2	3	17.7	63	32.4
PB	36	46	38.9	3	16.7	77	41.7
SA	687	34	22.3	10	22.4	50	23.4
HSM	594	21	8.8	9	20.5	37	13.5
AI	308	51	41.2	12	23.7	72	36.7
P		<.0001	<.001	.23	.69	<.0001	<.001

Note. *P* values for differences between medians within each set are based on the Kruskal-Wallis test, and *P* values for differences between percentages over specified number of days within each set are based on the χ^2 test.
[a]Abnormal finding in mammogram or clinical breast examination.
[b]Standard reporting categories from the Breast Imaging and Reporting Data System.[26] Neg = negative, Ben = benign, PB = probably benign, SA = suspicious abnormality, HSM = highly suggestive of malignancy, AI = assessment incomplete.

mammogram results (HSM, or "highly suggestive of malignancy") had much shorter diagnostic and total intervals, but treatment intervals did not vary significantly by mammography result.

Discussion

Delays between breast cancer screening and initiation of therapy are of prognostic concern if they permit tumor burdens to increase. Estimates for tumor doubling times range widely, with a median time of 260 days for mammographically detected tumors.[9] In this study, only 7.5% of the women had total intervals longer than 200 days. Unfortunately, no survival data are available to determine the significance of these prolonged intervals in our study population. An additional concern is the worry and anxiety women may experience before diagnosis.[15]

While our median diagnostic intervals are slightly longer than others have reported,[6,9] this is mainly because of the way dates are defined. NBCCEDP uses date of definitive pathologic diagnosis as the end of the diagnostic interval, whereas others use date of first diagnostic procedure.[9] Also, most studies include primarily symptomatic women, whose symptoms are usually analyzed sooner[6]; this is confirmed by our finding of symptomatic women experiencing shorter diagnostic intervals than asymptomatic women. Completeness of diagnostic follow-up for women followed up in our program is comparable to that of other programs.[9]

Since NBCCEDP serves women who are poor and uninsured, and pays for only some diagnostic and no treatment services, financial barriers may contribute to the longer diagnostic intervals. During a qualitative case study of 7 state-based programs, state program administrators and providers were concerned that this was a barrier to follow-up for some women. Since program participants were not questioned, we were unable to validate this concern.[16]

As expected, women with the most serious mammogram results received their breast cancer diagnoses promptly. Women with less definitive initial mammograms, such as those coded AI ("assessment incomplete"), might have experienced longer diagnostic intervals because additional mammographic views or ultrasound was needed to define the initial mammographic finding; only then would more definitive procedures be used to establish the diagnosis, if necessary.

Diagnostic intervals for women with normal mammograms and abnormal CBEs were longer than those for women with abnormal mammograms. When a mammogram is read as normal, health care providers and women may have a false sense of security and delay biopsy, as shown in reports of normal mammograms of palpable breast masses.[17–19] In one study where the median diagnostic interval was 17 days, symptomatic women with nonsuspicious mammograms had diagnostic intervals of 90 days or more.[19] In another study, 22% of women with palpable lesions eventually diagnosed as breast cancer had false-negative mammograms.[20] Therefore, biopsy of a suspicious breast mass should be done promptly, regardless of mammographic finding.[21]

Diagnostic and treatment intervals were shorter for Whites than for other racial and ethnic groups. To our knowledge, our results are the first to be based on differences among several racial and ethnic groups: earlier studies were limited to Whites vs Blacks or Whites vs other races.[22–24] The results seen here, however, may be confounded by programmatic differences in data collection, since the racial distributions are quite variable among programs.

Diagnostic and treatment intervals were shorter for rural women than urban women. Access to care or convenience of services may differ between the 2 groups. We had postulated that women living in rural areas who traveled great distances for breast screening and received abnormal results might well be referred for a surgical consult and a biopsy on that same day to minimize travel, while urban women with better geographic access to care might be brought back later for a surgical consult. Informants in the case study of 7 states corroborated this assumption.[25] However, our data suggested that rural women were no more likely than urban women to receive their entire diagnostic workup on the day of the screening.

Our results for treatment intervals, with a median of 10 days and approximately 80% of women initiating treatment within 30 days of diagnosis, are impressive, especially since treatment services are not reimbursed with federal funds. In a binational study of insured women, Katz and colleagues reported median intervals from diagnosis to initial surgical treatment of 6 days for women diagnosed in Canada and 10 days for women diagnosed in Washington State.[19] Another study found that one third of the women had treatment intervals greater than 6 weeks, while almost one quarter had treatment intervals of at least 12 weeks,[26] much longer than those seen here.

NBCCEDP provides one of the largest mammography series to date in the United States. The program targets a population that is often medically underserved, and the data collected reflect services actually delivered in a variety of community settings, including university- and community-based facilities, community health centers, health department clinics, and mobile mammography vans. The data are not collected for scientific investigation, but rather for program evaluation and assessment of service delivery. A limitation is that data collection may vary by screening program, even though detailed instructions for uniform, standardized data collection are distributed to programs. In addition, minimal information is collected by NBCCEDP on each woman, making it impossible to identify many of the factors (such as missed appointments or scheduling difficulties) that may be associated with longer intervals. Finally, our results could have been biased if some women lost to follow-up received breast cancer diagnoses outside the program. However, a comparison of women with incomplete follow-up and those with complete follow-up showed no differences in age, race/ethnicity, urban vs rural location, symptom status, or mammography results; thus, it is unlikely we introduced a major systematic bias by excluding the women lacking a final diagnosis.

The information provided here, although not generalizable to other programs, can be used by the CDC to evaluate and improve NBCCEDP. The program itself is the only federally funded program providing breast and cervical cancer screening for medically underserved women. The CDC implements many checks to ensure that program women are served appropriately, and it requires programs to establish proactive surveillance systems for timely and appropriate referral and follow-up of women with abnormal test results. In addition, new policies now allow state and tribal programs to reimburse for breast biopsies.[16] Furthermore, some states use multispecialty clinics, where women with abnormal screening results are seen by a radiologist and a surgeon on the same day, thereby reducing the need to return for follow-up.[25] Further investigation is warranted to evaluate these strategies and to better identify factors associated with long intervals, to shorten them, and thus to maximize the benefits of early detection. □

Contributors

L. S. Caplan planned the study, analyzed the data, and wrote the paper. D. S. May and L. C. Richards contributed significantly to both the analysis of the data and the writing of the paper.

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Physical Activity and Incident Diabetes Mellitus in Postmenopausal Women

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A B S T R A C T

Objectives. This study determined whether the incidence of diabetes is reduced among physically active older women.

Methods. We assessed physical activity by mailed questionnaire and 12-year incidence of diabetes (ostensibly type 2 diabetes) in a cohort of 34 257 women aged 55 to 69 years.

Results. After adjustment for age, education, smoking, alcohol intake, estrogen use, dietary variables, and family history of diabetes, women who reported any physical activity had a relative risk of diabetes of 0.69 (95% confidence interval = 0.63, 0.77) compared with sedentary women.

Conclusions. These findings suggest that physical activity is important for type 2 diabetes prevention among older women. (*Am J Public Health*. 2000;90:134–138)

The prevalence of type 2 diabetes has increased over the past 2 decades in the United States,[1] emphasizing the need for prevention. Adequate physical activity relative to energy intake prevents obesity, which is the major modifiable risk factor for diabetes. In addition, physical activity may independently enhance insulin sensitivity and glucose tolerance.[2–6] Ecologic data suggest that the population prevalence of diabetes is associated inversely with the average level of physical activity.[7,8] However, only a limited number of prospective studies have tested whether being physically active reduces the incidence of diabetes,[9–19] and only our previous, early report[11] focused on older women. In this article, we extend our follow-up to examine whether the incidence of type 2 diabetes was lower over 12 years in physically active women compared with inactive women.

Methods

Iowa Women's Health Study Cohort

In January 1986, we mailed a questionnaire about diet and lifestyle to 99 826 women aged 55 to 69 years who had a valid Iowa driver's license.[20–21] A total of 41 836 women completed and returned the questionnaire, of whom 99% were White, 77% were married, and 81% had a high school education or greater. Compared with nonrespondents, as ascertained from drivers' licenses, respondents were on average 3 months younger, 0.4 kg/m^2 lighter, and less likely to die of smoking-related diseases.[22] However, respondents and nonrespondents had a similar association of body mass index (BMI) with mortality and cancer incidence.[22]

Questionnaire

We asked women to report smoking status and amount, alcohol intake, use of estrogen replacement, family history of diabetes, height, and weight. We enclosed a tape measure so that a friend could measure the participant's waist (umbilical level) and hips (maximum). We assessed dietary habits by food frequency questionnaire. Previous analysis of diabetes in this cohort suggested that the intake of energy, intake of whole grains, and dietary fat, as reflected by the Keys' score, were important to consider as dietary covariates.[23] The questionnaire identified prevalent diabetes with the question "Has a doctor ever told you that you have diabetes mellitus (sugar diabetes)?" A validation study showed that of 44 Iowa women who self-reported diabetes, 28 (64%) cases were confirmed by their physician, and all of the reports of no diabetes (41) were confirmed.[11]

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We assessed leisure physical activity in 2 ways. First, we asked participants a general question about regular physical activity that has been used for 4 decades by the Gallup poll[24]: "Aside from any work you do at home or at a job, do you do anything regularly—that is, on a daily basis—that helps keep you physically fit?" Second, we asked participants how often they participate in moderate physical activity (e.g., bowling, golf, light sports or physical exercise, gardening, or taking long walks) or vigorous activity (e.g., jogging, racket sports, swimming, aerobics, or strenuous sports). Activities listed for moderate activity generally require 6.0 METs (work metabolic rate/resting metabolic rate) or less, whereas those listed for vigorous activity generally require more than 6.0 METs.[25] Response options for these questions ranged from "rarely or never" to "more than 4 times a week."

We considered responses to the questions assessing moderate and vigorous activity individually and also combined them as a 3-level (low, medium, and high) physical activity index based on frequency and intensity of activity. Women who reported participating in vigorous activity 2 or more times per week or those who reported participating in moderate physical activity more than 4 times per week composed the high category. Women who reported participating in vigorous activity once a week or moderate activity 1 to 4 times per week composed the medium category. The remaining women, who reported participating in vigorous or moderate activity never or a few times a month, composed the low physical activity category.

Ascertainment of End Points

We followed the cohort via mailed questionnaires in 1987 (91% response), 1989 (89%), 1992 (83%), and 1997 (79%) and identified deaths through the State Health Registry of Iowa and the National Death Index. We defined incident diabetes mellitus as occurring if a woman reported a new diagnosis of diabetes made by a physician. Because age at onset was older than 55 years, we presumed that virtually all diagnoses were type 2 diabetes. We computed person-time for diabetes cases as the sum of the known disease-free period plus half of the period during which the diagnosis was first made. We considered those who consistently answered "no" or "don't know" as not having incident diabetes. We censored the follow-up for women who stopped answering the questionnaires at the date of their last completed questionnaire. Otherwise, we censored women when they died or at the date of the 1997 questionnaire.

TABLE 1—Baseline Risk Factors, by Physical Activity Category: Iowa Women's Health Study

Characteristics	Physical Activity Index		
	Low (n = 16 032)	Medium (n = 9579)	High (n = 8646)
Prevalence, %			
Body mass index ≥ 28 kg/m^2	39	31	25
Waist-to-hip ratio ≥ 0.85	45	37	31
Current smoker	20	13	10
Alcohol user	43	49	48
Education level > high school	35	42	46
Current estrogen use	10	11	12
Family history of diabetes	22	22	23
Mean			
Energy intake, kcal/day	1792	1813	1811
Whole grain intake, servings/day	10	12	13
Keys' score	18.6	18.5	18.4

Data Analysis

We excluded from analysis women who were not postmenopausal at baseline (n = 569), who did not answer any of the questions pertaining to physical activity (n = 231), or who answered "yes" to the prevalent diabetes question (n = 3002). Notably, this prevalence of diabetes (3002/41 836) was in the range expected from other studies.[1] These overlapping exclusions left 38 091 women eligible for follow-up; 34 257 had complete data on all covariates.

We used proportional hazards regression to compute relative risks (RRs), 95% confidence intervals (CIs), and *P* values for trend in relative risks. No evidence indicated that proportional hazards assumptions were violated. We created 3 models; the first adjusted for age only. The second, our primary model, adjusted for several potential confounding variables: age, alcohol intake (none, <4 g/day, ≥4 g/day), total energy intake (quintiles), whole grain intake (quintiles), Keys' score (quintiles), cigarette smoking status (current, past, never) and pack-years, use of estrogen replacement therapy (never, former, current), education level (did not graduate from high school, high school graduate, more than high school graduate), and first-degree female relative with diabetes (yes, no, unknown). The age-adjusted and primary models gave similar results, so only the primary model is shown.

The third model, a secondary model, adjusted further for BMI (quintiles) and waist-to-hip ratio (quintiles). Because physical activity may directly influence BMI and waist-to-hip ratio, the relative risk from this model indicates the degree to which physical inactivity might contribute to diabetes in ways other than causing obesity.

Results

Compared with women in the low physical activity category, women in the 2 higher physical activity categories were less likely to be overweight, to have a high waist-to-hip ratio, and to be smokers; they were more likely to drink alcohol, to be educated beyond high school, and to take replacement estrogen (Table 1). The 2 higher physical activity groups also had a higher mean intake of energy and whole grains than the low-activity group.

Over approximately 350 000 person-years of follow-up, 1997 women reported the new onset of diabetes. Diabetes incidence was associated positively with age, pack-years of smoking, energy intake, Keys' score, BMI, waist-to-hip ratio, and family history of diabetes; it was associated negatively with education level, alcohol intake, estrogen use, and whole grain intake (data not shown). Compared with those reporting no regular physical activity, those regularly engaging in physical activity had a relative risk of diabetes of 0.69 (95% CI = 0.63, 0.77) after adjustment for major confounding variables in our primary model (Table 2). As expected, adjustment for BMI and waist-to-hip ratio in our secondary model attenuated this relative risk to 0.86 (95% CI = 0.78, 0.95). Frequency of both moderate physical activity and vigorous physical activity showed strong monotonic negative associations with diabetes incidence, so the most frequently active women had half the risk of diabetes as the least frequently active (Table 2).

In a supplemental analysis (data not shown) focusing on the 26 124 women who reported no vigorous activity, moderate activity was still associated negatively with diabetes: relative risks for moderate activity rarely/never, once per week to a few times per

TABLE 2—Relative Risk (RR) of Diabetes According to Level of Physical Activity Among 34 257 Postmenopausal Women in Iowa, 1986–1997

	Incident Diabetes (n)	Person-Years	Primary Model[a] RR	Primary Model[a] (95% CI)	Secondary Model[b] RR	Secondary Model[b] (95% CI)
Regular physical activity						
No	1343	199 993	1.0		1.0	
Yes	654	149 300	0.69	(0.63, 0.77)	0.86	(0.78, 0.95)
Moderate physical activity						
Rare or never	553	66 410	1.0		1.0	
Once/week or few times/month	617	99 035	0.80	(0.71, 0.90)	0.90	(0.79, 1.01)
2–4 times/week	548	110 240	0.65	(0.58, 0.74)	0.86	(0.76, 0.98)
>4 times/week	294	75 156	0.51	(0.43, 0.59)	0.73	(0.62, 0.85)
P for trend				<.001		<.001
Vigorous physical activity						
Rare or never	1755	286 262	1.0		1.0	
Once/week or few times/month	130	31 269	0.76	(0.63, 0.92)	0.92	(0.76, 1.10)
2–4 times/week	86	22 833	0.68	(0.54, 0.86)	0.88	(0.70, 1.11)
>4 times/week	24	8 482	0.46	(0.29, 0.72)	0.64	(0.41, 1.01)
P for trend				<.001		<.05
Physical activity index						
Low	1135	158 739	1.0		1.0	
Medium	496	98 412	0.75	(0.67, 0.84)	0.91	(0.82, 1.02)
High	358	90 620	0.58	(0.51, 0.66)	0.79	(0.70, 0.90)
P for trend				<.001		<.001

Note. CI = confidence interval.
[a]Adjusted for age, education, smoking, alcohol intake, estrogen replacement, energy intake, whole grain intake, Keys' score, and family history of diabetes.
[b]Also adjusted for body mass index and waist-to-hip ratio.

month, 2 to 4 times per week, and more than 4 times per week were 1.0, 0.79, 0.66, and 0.57 (*P* for trend<.001), respectively, adjusted for the covariates in our primary model.

The physical activity index, which combined moderate and vigorous activity frequencies, also was associated negatively and strongly with diabetes incidence (RR = 0.58 comparing high to low activity in the primary model; 95% CI = 0.51, 0.66) (Table 2). This association was similar across the 3 strata of baseline age (55–59, 60–64, and 65–69 years) and 3 strata of baseline BMI (<25, 25–29.99, and ≥ 30 kg/m^2) (Table 3).

We repeated these analyses after excluding people who reported at baseline a history of heart attack, angina, or other heart disease. Relative risks were virtually identical to those in Tables 2 and 3.

Discussion

We found that greater leisure time physical activity was associated with a reduced risk of type 2 diabetes over 12 years of follow-up in a prospective cohort of older women. The association was strong and graded, such that the risk of diabetes was approximately halved in the most active vs the least active women. This finding was similar to a report of 2-year findings in this cohort,[11] but the previous report did not focus specifically on physical activity and adjusted only for age.

In the present report, the association of physical activity with diabetes proved to be independent of age, education level, smoking, alcohol intake, estrogen replacement, energy intake, whole grain intake, Keys' score, and family history of diabetes. It is not surprising that adjustment for BMI and waist-to-hip ratio, both strong diabetes risk factors, attenuated the observed association. This result is consistent with the theory that physical activity at least partly prevents diabetes by reducing adiposity. Lower adiposity improves insulin sensitivity and glucose tolerance and reduces free fatty acid levels.[2–6,26] Other possible mechanisms by which physical activity may improve insulin sensitivity and glucose tolerance include increased skeletal muscle mass, increased muscle blood flow, greater insulin receptor density, increased glucose transporter protein levels, enhanced skeletal muscle glucose disposal, and improved muscle fiber type and capillary density.[26]

Our results are consistent with those of most previous prospective studies of physical activity and type 2 diabetes,[9,10,12–19] which primarily studied men and younger women. The results are also consistent with those of 2 prospective studies showing that low cardiorespiratory fitness is a risk factor for diabetes in men.[17,27] Relative risks for physically active vs inactive participants typically have ranged between 0.4 and 0.8, although some studies found that the association was statistically nonsignificant in certain race groups and between sexes.[13,15] Other studies,[9,10,14,16,17] but not all,[12,19] have reported, as in this study, a dose–response relation between the amount of physical activity and the degree of reduction in diabetes risk.

Some studies have reported that physical activity may be more beneficial for obese or for other persons at increased risk for diabetes.[9,12,17] However, other studies have suggested that physical activity or fitness may be less[14] beneficial for obese persons than for nonobese persons or equally[10,27] beneficial for both. We found no difference in relative risks by BMI (Table 3) or by age (55–69 years).

Consensus panels have concluded that regular vigorous physical activity affords the greatest health benefits, but even moderate physical activity may offer significant benefits.[28,29] Studies vary widely in how they assess intensity of activity, and it has been unclear whether a threshold intensity of physical activity is required for diabetes prevention.[9,16,17,19] We found that even among those reporting no vigorous activity, a greater frequency of moderate activity was associated with lower diabetes risk. This finding may be particularly important for older women, who infrequently participate in vigorous sports.

TABLE 3—Age-Specific or Body Mass Index (BMI)–Specific, Multivariable-Adjusted[a] Relative Risk (RR) of Diabetes According to Level of Physical Activity Among 34 257 Postmenopausal Women in Iowa, 1986–1997

	Age Group, y											
	55–59				60–64				65–69			
	Incident Diabetes (n)	Person-Years	RR	(95% CI)	Incident Diabetes (n)	Person-Years	RR	(95% CI)	Incident Diabetes (n)	Person-Years	RR	(95% CI)
Physical activity index												
Low	390	61 496	1.0		404	56 421	1.0		341	40 823	1.0	
Medium	163	35 473	0.76	(0.62, 0.92)	165	34 610	0.73	(0.60, 0.88)	168	28 329	0.76	(0.62, 0.93)
High	117	31 523	0.62	(0.50, 0.78)	126	32 502	0.58	(0.47, 0.71)	115	26 595	0.54	(0.43, 0.68)
P for trend			<.001				<.001				<.001	
	BMI, kg/m^2											
	<25				25–29.99				≥30			
	Incident Diabetes (n)	Person-Years	RR	(95% CI)	Incident Diabetes (n)	Person-Years	RR	(95% CI)	Incident Diabetes (n)	Person-Years	RR	(95% CI)
Physical activity index												
Low	111	59 380	1.0		375	58 650	1.0		649	40 710	1.0	
Medium	76	42 270	1.01	(0.74, 1.38)	171	38 213	0.74	(0.61, 0.90)	249	17 928	0.89	(0.76, 1.04)
High	57	44 137	0.75	(0.53, 1.05)	143	33 913	0.70	(0.56, 0.85)	158	12 570	0.77	(0.63, 0.92)
P for trend			.09				.0005				.005	

Note. CI = confidence interval.
[a]Adjusted for age, education, smoking, alcohol intake, estrogen replacement, energy intake, whole grain intake, Keys' score, and family history of diabetes.

Limitations of our study warrant consideration. The baseline response rate was 42%, but respondents and nonrespondents had similar mean age and BMI and similar associations of BMI with incident disease.[22] Therefore, it seems unlikely that the low baseline response rate would render associations between physical activity and diabetes biased or nongeneralizable.

The physical activity questionnaire was brief. Although the questionnaire asked about the frequency of moderate and vigorous physical activity, it did not assess the duration of usual physical activities. We also asked about current physical activity, not lifelong activity. However, current physical activity is relevant because the effects of physical activity on insulin sensitivity appear to reverse quickly when activity ceases.[26] The physical activity questionnaire has not been validated, although we have shown inverse associations between our physical activity measures and coronary heart disease mortality in this cohort.[30]

We assessed diabetes by self-report, as have many previous prospective studies of physical activity and diabetes. The prevalence of women who reported diabetes at baseline (and were excluded) was in the range expected from other studies.[1] Yet, our validation study (see the Methods section earlier in this article) suggested that participants overreported diabetes compared with physician diagnoses. However, the new American Diabetes Association criteria have lowered the threshold for diabetes to a fasting glucose level greater than 125 mg/dL,[31] so women's overreports of diabetes may have been fewer than the validation study suggested. Another study reported reasonable validity of self-reports of diabetes,[32] although, clearly, early diabetes often is undiagnosed.

All of the above errors should have been random, thus lessening our ability to show an association between physical activity and diabetes. We probably also made errors in measurement of confounding variables in our study. If so, this would have led to residual confounding and a possible exaggeration of the relation between physical activity and diabetes.

The prevalence of type 2 diabetes has risen substantially in the United States in recent decades.[1] Physical inactivity and obesity are potentially modifiable risk factors for type 2 diabetes. If, as in this study (Table 2), the relative risk of not being active daily is 1.0/0.86 (1.16) and the prevalence of not being active daily is 57%, then attributable fraction calculations[33] suggest that up to 8% of cases of diabetes in inactive older women might be prevented if they began regular physical activity. An even higher percentage might be prevented if the physical activity led to substantial weight

loss. Currently, the National Institute of Diabetes and Digestive and Kidney Diseases is sponsoring a multicenter clinical trial for the primary prevention of type 2 diabetes.[34] If sufficient lifestyle change can be achieved, this trial could provide even better evidence for the role of physical activity in the prevention of type 2 diabetes. □

Contributors

A. R. Folsom planned the study and prepared the paper. L. H. Kushi planned the study and contributed to the writing of the paper. C.-P. Hong performed the data analysis and contributed to the writing of the paper.

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