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Authors

Luo, J
Margolis, KL
Adami, H-O
et al.

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Short Communication

Obesity and risk of pancreatic cancer among postmenopausal women: the Women's Health Initiative (United States)

J Luo*[,1,2], KL Margolis[3], H-O Adami[2,4], A LaCroix[5] and W Ye[2], For the Women's Health Initiative Investigators

[1]Institute of Social Development and Public Policy, Beijing Normal University, Beijing, China; [2]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; [3]HealthPartners Research Foundation, Minneapolis, MN, USA; [4]Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA; [5]Department of Epidemiology, University of Washington, Seattle, WA, USA

A total of 138 503 women in the Women's Health Initiative in the United States were followed (for an average of 7.7 years) through 12 September 2005 to examine obesity, especially central obesity in relation to pancreatic cancer ($n = 251$). Women in the highest quintile of waist-to-hip ratio had 70% (95% confidence interval 10–160%) excess risk of pancreatic cancer compared with women in the lowest quintile.

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Pancreatic cancer ranks as the fourth leading cause of cancer death in the United States (Ekbom and Hunter, 2007). Besides tobacco smoking and chronic pancreatitis (Lowenfels *et al*, 1999), little is known of its aetiology, but recently, increasing evidence has suggested that obesity is a risk factor (Berrington de Gonzalez *et al*, 2003; Larsson *et al*, 2007). However, in most studies, the association seems to be weaker in women – who tend to gain weight more peripherally – than in men, suggesting that central adiposity may be a stronger risk factor for pancreatic cancer than body mass index (BMI). Few studies have investigated this aspect and the findings are inconsistent (Larsson *et al*, 2005; Sinner *et al*, 2005; Ansary-Moghaddam *et al*, 2006; Berrington de Gonzalez *et al*, 2006).

We have used the large prospective Women's Health Initiative (WHI) study, with measured anthropometric factors, including hip and waist circumference, to examine the relationship between BMI, central adiposity, and pancreatic cancer risk.

MATERIALS AND METHODS

Women's Health Initiative

The WHI, an ongoing, ethnically and geographically diverse, multi-centre clinical trial (CT) and observational study (OS), was designed to address some of the major causes of morbidity and mortality in postmenopausal women. Briefly, a total of 161 808 women aged 50–79 years were recruited at 40 clinical centres throughout the United States from 1 September 1993 through 1998. The WHI includes three overlapping CT components (hormone trial, dietary modification trial, and calcium/vitamin D supplementation trial) and an OS. All participants in WHI gave informed consent and were followed prospectively. Details of the scientific rationale, eligibility requirements and baseline characteristics of the participants in the WHI have been published elsewhere (Hays *et al*, 2003; Jackson *et al*, 2003; Langer *et al*, 2003; Ritenbaugh *et al*, 2003; Stefanick *et al*, 2003).

The following participants were excluded from the original cohort of 161 808 : 14 849 with a history of cancer (except non-melanoma skin cancer) at baseline, 668 with no follow-up, 7491 with missing values of main exposures and confounders (including weight, height, waist circumference, hip circumference, smoking, and diabetes), and 297 (0.18%) with waist-to-hip ratio (WHR) values of beyond 4 s.d. (WHR < 0.4 or WHR > 1.2), leaving 138 503 women for analysis.

All exposures in our analyses were collected at baseline for all participants. During the baseline clinical visit, trained and certified staff performed anthropometric measurements, including height, weight, hip and waist circumferences, and blood pressure. Body mass index was calculated as weight in kilograms divided by the square of height in metres. Waist circumference at the natural waist or narrowest part of the torso and hip circumference at the maximal circumference were measured to the nearest 0.1 cm. WHR was computed as the ratio of these two measurements. Weight changes during the participant's adult lives were obtained by self-report questionnaire, categorized as weight stayed stable (within 10 lb), steady gain in weight, lost weight as an adult and kept it off, and weight has gone up and down again by more than 10 lb.

Information on demographic characteristics, medical history, and personal habits (lifestyle) were obtained by interview or by self-report using standardized questionnaires including age at enrolment (<55, 55–59, 60–64, 65–69, 70–74, 75–), smoking status (never, past, current) with information on how many years since quitting for past smokers and how many cigarettes smoked per day for ever smokers, physical activity and history of hypertension and diabetes while not pregnant.

*Correspondence: Dr J Luo, Institute of Social Development and Public Policy, Beijing Normal University, Beijing 100875, China;
E-mail: luojuhua8@yahoo.com
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Women in the CT were followed through regularly scheduled examinations to ensure timely ascertainment of updated medical histories. All women in the CT were expected to attend annual clinical visits, with intermediate 6-month mail, phone or clinical contacts. The OS participants were contacted annually by mailed self-administered questionnaires. The completion rate of OS annual questionnaires was 93–96%. In this analysis, all participants were followed up until 12 September 2005. Initial reports of cancer were ascertained by self-administered questionnaires, and all self-reports of pancreatic cancer were confirmed by review of medical records, including pathology reports (if a biopsy or resection was done).

Statistical analyses

The hazard ratio (HR) for pancreatic cancer was estimated using the Cox proportional hazards model. Different study cohorts (participation in OS or CTs, and different treatment assignments for all three CTs) were treated as strata in the model. In the multivariable models, we adjusted for age, smoking status (never, former smoking (quitted time $\geqslant$30 years, 20–29, 10–19, and $<$10 years), and current smoking ($<$4, 5–14, 15–24, 25 and more cigarettes per day)). As diabetes could be in the causal pathway between obesity and risk, we performed analyses (both adjusted and unadjusted) for this factor.

We treated anthropometric measures as categorical (in quintiles) variables in the regression models, except BMI which was categorized ($<$22, 22–$<$25, 25–$<$30, 30–$<$35, and $\geqslant$35 kg m^{-2}). Tests for trend were performed by creating a continuous variable from the medians of the categories. In addition, to eliminate undiagnosed cases that might have experienced weight loss before completing the baseline questionnaires, we also performed analyses that excluded the first 2 years of follow-up. The proportional assumption was satisfied for all exposure variables of interest and potential confounding variables based on graphs of scaled Schoenfeld residuals (Hess, 1995).

RESULTS

As of 12 September 2005 with an average 7.7 years of follow-up, 251 incident cases of pancreatic cancer had been identified. Characteristics at baseline of selected variables by quintile of WHR are shown in Table 1. Compared with women with lower WHR, those with higher WHR were older, non-white, and less educated. Women with higher WHR were also more likely to be past or current smokers and tended to smoke more cigarettes per day and to have quit more recently, to have higher total energy intake, be less physically active, and have higher prevalence of diabetes and hypertension. WHR was positively associated with weight, BMI, waist and hip circumference.

Among the tested anthropometric variables, only WHR was significantly associated with the risk of pancreatic cancer. After adjusting for potential confounders, women in the highest quintile of WHR had 70% (95% CI 10–160%) excess risk compared with women in the lowest quintile of WHR. When WHR was analyzed as a continuous variable, risk increased by 27% (95% CI 7–50%) per 0.1 increase. No association was observed between pancreatic cancer risk and other anthropometric variables, including height, BMI, hip circumference, waist circumference, and weight changes during adult life (Table 2).

Finally, we repeated all the above analyses with the exclusion of the first 2 years of follow-up; findings remained broadly similar to

Table 1 Baseline characteristics of participants in relation to WHR (quintiles) among 138 503 postmenopausal women[a]

	WHR (quintile, range)				
Variable	**1 (0.40–0.75)**	**2 (0.75–0.79)**	**3 (0.79–0.82)**	**4 (0.82–0.87)**	**5 (0.87–1.20)**
Total number of women	27 707	27 694	27 736	27 651	27 715
Age at baseline (mean, years)	61.4	62.7	63.3	63.7	64.2
White, non-Hispanic-ethnicity (%)	86.9	84.3	82.0	79.6	79.6
College graduate or above education (%)	48.1	43.1	38.3	34.9	31.3
Ever smoking (%)					
Past	37.6	39.2	40.1	41.1	42.8
Quit $<$20 years(%)	41.4	44.3	46.5	51.3	54.5
Current	5.0	6.7	7.2	7.8	8.9
$\geqslant$15 cigarettes day^{-1} (%)	40.4	43.3	48.5	49.3	53.9
Dietary intake (mean)					
Total energy intake (kcal day^{-1})	1580	1611	1638	1679	1727
Fruit and vegetable(median servings per day)	4.3	4.2	4.1	3.9	3.9
Physical activity (METs per week)	15.2	13.8	12.3	11.0	9.7
Diabetes mellitus (%)	1.4	2.3	4.0	6.9	14.2
Hypertension (%)	19.4	26.0	32.5	39.5	48.8
Weight (kg, mean)	65.5	69.1	72.8	77.1	81.8
Height (cm, Mean)	162.4	162.0	161.7	161.5	161.5
BMI (kg m^{-2}, mean)	24.9	26.3	27.8	29.5	31.3
Waist circumference (mean, cm)	73.8	80.2	85.6	91.8	100.8
Hip circumference (mean, cm)	103.3	104.5	106.5	108.7	109.5
WHR (mean)	0.71	0.77	0.80	0.85	0.92
Type of weight change					
Steady gain in weight	23.6	30.3	34.4	38.0	39.6
Lost weight and kept it off	4.3	3.0	2.2	1.8	1.4
Weight upon and down (more than 10 lb)	27.6	31.0	34.3	37.4	41.1

BMI = body mass index; MET = metabolic equivalent tasks; WHR = waist-to-hip ratio. [a]All comparisons of cohort characteristics by waist-to-hip levels are significantly different, with $P<0.0001$ based on χ^2 test for categorical variables and analysis of variance (ANOVA) test for continuous variables.

Epidemiology

Table 2 Age-adjusted and multivariate-adjusted HR of pancreatic cancer by baseline measures of adiposity among 138 503 postmenopausal women

Variable	No. of cases	Age-adjusted HR (95% CI)	Multi-adjusted HR (95% CI)[a]	Multi-adjusted HR (95% CI)[b]
Height (cm)				
1 (100.0–156.4, 153.6)	63	Reference	Reference	Reference
2 (156.5–160.1, 158.5)	54	1.0 (0.7–1.4)	0.9 (0.6–1.3)	0.9 (0.6–1.3)
3 (160.2–163.4, 161.9)	48	0.9 (0.6–1.3)	0.8 (0.6–1.2)	0.8 (0.6–1.2)
4 (163.5–167.0, 165.1)	43	0.9 (0.6–1.2)	0.8 (0.5–1.1)	0.8 (0.5–1.1)
5 (167.1–212.0, 170.0)	43	0.9 (0.6–1.3)	0.9 (0.6–1.3)	0.9 (0.6–1.3)
P (trend)		0.4	0.3	0.3
BMI (kg m^{-2})				
<22.0	25	0.8 (0.5–1.2)	0.8 (0.5–1.2)	0.8 (0.5–1.2)
22.0–24.9	62	Reference	Reference	Reference
25.0–29.9	84	0.9 (0.6–1.2)	0.9 (0.6–1.2)	0.9 (0.6–1.2)
30.0–34.9	56	1.2 (0.8–1.7)	1.1 (0.8–1.6)	1.1 (0.7–1.5)
35.0–	24	0.9 (0.6–1.4)	0.9 (0.5–1.4)	0.8 (0.5–1.3)
P (trend)		0.4	0.5	0.9
Hip (cm) quintile (range, median)				
1 (40.0–96.9, 93.0)	52	Reference	Reference	Reference
2 (97.0–101.9, 99.0)	58	1.2 (0.8–1.7)	1.2 (0.8–1.8)	1.2 (0.8–1.8)
3 (102.0–107.1, 104.3)	50	1.0 (0.6–1.4)	1.0 (0.6–1.4)	0.9 (0.6–1.4)
4 (107.1–115.0, 111.0)	42	0.9 (0.6–1.3)	0.9 (0.6–1.3)	0.8 (0.6–1.3)
5 (115.1–200.0, 122.5)	49	1.1 (0.7–1.6)	1.1 (0.7–1.6)	1.0 (0.7–1.5)
P (trend)		0.7	0.6	0.4
Waist (cm) quintile (range, median)				
1 (35.0–74.5, 70.5)	41	Reference	Reference	Reference
2 (74.6–81.0, 78.0)	50	1.2 (0.8–1.7)	1.1 (0.7–1.7)	1.1 (0.7–1.7)
3 (81.1–88.0, 85.0)	46	1.1 (0.7–1.6)	1.0 (0.7–1.6)	1.0 (0.7–1.6)
4 (88.1–97.4, 92.4)	63	1.5 (1.0–2.2)	1.4 (1.0–2.1)	1.4 (0.9–2.0)
5 (97.5–194.2, 105.0)	51	1.3 (0.9–1.9)	1.2 (0.8–1.8)	1.1 (0.7–1.6)
P (trend)		0.1	0.2	0.6
Waist as continuous (per 10 cm)	251	1.10 (1.00–1.20)	1.08 (0.98–1.18)	1.05 (0.95–1.15)
WHR quintile (range, median)				
1 (0.40–0.75, 0.72)	34	Reference	Reference	Reference
2 (0.75–0.79, 0.77)	47	1.3 (0.8–2.0)	1.3 (0.8–1.9)	1.2 (0.8–1.9)
3 (0.79–0.82, 0.80)	44	1.2 (0.7–1.8)	1.1 (0.7–1.7)	1.1 (0.7–1.7)
4 (0.82–0.87, 0.84)	48	1.2 (0.8–1.9)	1.2 (0.7–1.8)	1.1 (0.7–1.7)
5 (0.87–1.20, 0.91)	78	2.0 (1.4–3.0)	1.8 (1.2–2.8)	1.7 (1.1–2.6)
P (trend)		0.0003	0.002	0.01
WHR as continuous (per 0.1)	251	1.38 (1.17–1.63)	1.32 (1.12–1.56)	1.27 (1.07–1.50)
Type of weight change				
Stable weight	85	Reference	Reference	Reference
Steady gain in weight	77	0.9 (0.7–1.2)	0.9 (0.7–1.2)	0.9 (0.6–1.2)
Lost weight and kept it off	5	0.7 (0.3–1.6)	0.6 (0.3–1.6)	0.6 (0.3–1.5)
Weight up and down (more than 10 lb)	83	1.0 (0.7–1.3)	0.9 (0.7–1.3)	0.9 (0.7–1.2)

CI = confidence interval; HR = hazard ratio; WHR = waist-to-hip ratio. [a]Adjusted variables included age, different treatment assignments in clinical trials, and smoking status (never, former smoking (quitted time ⩾ 30years, 20- < 30, 10- < 20, < 10 years), and current smoking (< 4, 5–14, 15–24, 25 and more cigarettes per day)). [b]Further adjusted for diabetes history at baseline.

those from the full analyses with RR = 1.6 (95% CI: 1.0–2.6) comparing women in the highest to the lowest of WHR.

DISCUSSION

In this large prospective study, we observed that central obesity measured by high WHR, rather than general obesity measured by high BMI, was associated with an increased risk of developing pancreatic cancer among postmenopausal women.

Our result is consistent with most earlier studies for central adiposity and pancreatic cancer (Larsson *et al*, 2005; Patel *et al*, 2005; Ansary-Moghaddam *et al*, 2006; Berrington de Gonzalez *et al*, 2006), although not all (Sinner *et al*, 2005). In particular, the large prospective European prospective investigation into cancer and nutrition (EPIC) study (Berrington de Gonzalez *et al*, 2006) also observed significant increased risk associated with higher WHR (HR = 1.24 (1.04–1.48) per 0.1 increase of WHR), but not with BMI. In fact, there was a weak or no association among women in all but 4 (Michaud *et al*, 2001; Calle *et al*, 2003; Pan *et al*, 2004; Patel *et al*, 2005) of the 16 studies published since 2000 on the association between the risk of pancreatic cancer and BMI that included women (Coughlin *et al*, 2000; Gapstur *et al*, 2000; Nilsen and Vatten, 2000; Hanley *et al*, 2001; Michaud *et al*, 2001; Wolk *et al*, 2001; Calle *et al*, 2003; Pan *et al*, 2004; Eberle *et al*, 2005; Fryzek *et al*, 2005; Larsson *et al*, 2005; Patel *et al*, 2005; Rapp *et al*, 2005; Sinner *et al*, 2005; Lin *et al*, 2007; Nothlings *et al*, 2007).

The link between obesity and pancreatic cancer – similar to the plausible mechanism between diabetes and pancreatic cancer – may arise as a result of elevated fasting and postprandial glucose concentration, hyperinsulinemia, or both (Everhart and Wright, 1995; Gapstur *et al*, 2000; Batty *et al*, 2004; Jee *et al*, 2005). Many experimental studies (Pour and Stepan, 1984; Pour *et al*, 1990; Schneider *et al*, 2001; Wang *et al*, 2003; Hennig *et al*, 2004) and

observational studies (Everhart and Wright, 1995; Gapstur *et al*, 2000; Huxley *et al*, 2005; Stolzenberg-Solomon *et al*, 2005) support the biological plausibility of higher insulin concentrations and insulin resistance in promoting pancreatic cancer development. If the induced insulin resistance is the underlying mechanism through which obesity increases the risk, then it is not surprising that we observed a stronger association with WHR abdominal adiposity than with BMI among postmenopausal women, because central adiposity is more strongly associated with glucose intolerance and increased insulin levels (Carey *et al*, 1997; Van Pelt *et al*, 2001; Sierra-Johnson *et al*, 2004; Tanko *et al*, 2004). In addition, the body fat distribution changes significantly following menopause, with a shift from preferential storage in gluteal/femoral regions to abdominal depots. Thus, our finding further suggests that the central adiposity is a better predictor of disease risk than BMI in postmenopausal women (Van Pelt *et al*, 2001).

Strengths of our study include the prospective design, the large size of the cohort, the reasonably large number of cases, the high prevalence of obesity, including central adiposity, the detailed information on potential confounders, and the precise measurement of anthropometric factors. Measurement rather than self-reporting is particularly important for waist and hip circumferences, which are likely to be reported less accurately than height and weight. There is a possibility of misclassification among the cases, given the difficulty in diagnosis of this disease. However, this misclassification is likely to be non-differential with respect to anthropometric measurements, which may make our results conservative. A second possibility was weight loss because of undiagnosed disease, but results did not change after excluding the first 2 years of follow-up. It is unlikely that pancreatic cancer advanced enough to cause weight loss would remain undiagnosed for more than 2 years.

In conclusion, our large prospective study shows that increased central adiposity was associated with an increased risk of developing pancreatic cancer among postmenopausal women.

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REFERENCES

Ansary-Moghaddam A, Huxley R, Barzi F, Lawes C, Ohkubo T, Fang X, Jee SH, Woodward M (2006) The effect of modifiable risk factors on pancreatic cancer mortality in populations of the Asia-Pacific region. *Cancer Epidemiol Biomarkers Prev* **15:** 2435 – 2440

Batty GD, Shipley MJ, Marmot M, Smith GD (2004) Diabetes status and post-load plasma glucose concentration in relation to site-specific cancer mortality: findings from the original Whitehall study. *Cancer Causes Control* **15:** 873 – 881

Berrington de Gonzalez A, Spencer EA, Bueno-de-Mesquita HB, Roddam A, Stolzenberg-Solomon R, Halkjaer J, Tjonneland A, Overvad K, Clavel-Chapelon F, Boutron-Ruault MC, Boeing H, Pischon T, Linseisen J, Rohrmann S, Trichopoulou A, Benetou V, Papadimitriou A, Pala V, Palli D, Panico S, Tumino R, Vineis P, Boshuizen HC, Ocke MC, Peeters PH, Lund E, Gonzalez CA, Larranaga N, Martinez-Garcia C, Mendez M, Navarro C, Quiros JR, Tormo MJ, Hallmans G, Ye W, Bingham SA, Khaw KT, Allen N, Key TJ, Jenab M, Norat T, Ferrari P, Riboli E (2006) Anthropometry, physical activity, and the risk of pancreatic cancer in the European prospective investigation into cancer and nutrition. *Cancer Epidemiol Biomarkers Prev* **15:** 879 – 885

Berrington de Gonzalez A, Sweetland S, Spencer E (2003) A meta-analysis of obesity and the risk of pancreatic cancer. *Br J Cancer* **89:** 519 – 523

Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ (2003) Overweight, obesity, and mortality from cancer in a prospectively studied cohort of US adults. *N Engl J Med* **348:** 1625 – 1638

Carey VJ, Walters EE, Colditz GA, Solomon CG, Willett WC, Rosner BA, Speizer FE, Manson JE (1997) Body fat distribution and risk of non-insulin-dependent diabetes mellitus in women. The Nurse's Health Study. *Am J Epidemiol* **145:** 614 – 619

Coughlin SS, Calle EE, Patel AV, Thun MJ (2000) Predictors of pancreatic cancer mortality among a large cohort of United States adults. *Cancer Causes Control* **11:** 915 – 923

Eberle CA, Bracci PM, Holly EA (2005) Anthropometric factors and pancreatic cancer in a population-based case – control study in the San Francisco Bay area. *Cancer Causes Control* **16:** 1235 – 1244

Ekbom A, Hunter D (2007) Pancreatic cancer. In *Textbook of cancer epidemiology*, Adami HO, Hunter D, Trichopoulos D (eds), pp 233 – 247. New York: Oxford University Press Inc

Everhart J, Wright D (1995) Diabetes mellitus as a risk factor for pancreatic cancer. A meta-analysis. *JAMA* **273:** 1605 – 1609

Fryzek JP, Schenk M, Kinnard M, Greenson JK, Garabrant DH (2005) The association of body mass index and pancreatic cancer in residents of southeastern Michigan, 1996 – 1999. *Am J Epidemiol* **162:** 222 – 228

Gapstur SM, Gann PH, Lowe W, Liu K, Colangelo L, Dyer A (2000) Abnormal glucose metabolism and pancreatic cancer mortality. *JAMA* **283:** 2552 – 2558

Hanley AJ, Johnson KC, Villeneuve PJ, Mao Y (2001) Physical activity, anthropometric factors and risk of pancreatic cancer: results from the Canadian enhanced cancer surveillance system. *Int J Cancer* **94:** 140 – 147

Hays J, Hunt JR, Hubbell FA, Anderson GL, Limacher M, Allen C, Rossouw JE (2003) The Women's Health Initiative recruitment methods and results. *Ann Epidemiol* **13:** S18 – S77

Hennig R, Ding XZ, Adrian TE (2004) On the role of the islets of Langerhans in pancreatic cancer. *Histol Histopathol* **19:** 999 – 1011

Hess KR (1995) Graphical methods for assessing violations of the proportional hazards assumption in Cox regression. *Stat Med* **14:** 1707 – 1723

Huxley R, Ansary-Moghaddam A, Berrington de Gonzalez A, Barzi F, Woodward M (2005) Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. *Br J Cancer* **92:** 2076 – 2083

Jackson RD, LaCroix AZ, Cauley JA, McGowan J (2003) The Women's Health Initiative calcium/vitamin D trial: overview and baseline characteristics of participants. *Ann Epidemiol* **13:** S98 – S106

Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM (2005) Fasting serum glucose level and cancer risk in Korean men and women. *JAMA* **293:** 194 – 202

Langer RD, White E, Lewis CE, Kotchen JM, Hendrix SL, Trevisan M (2003) The Women's Health Initiative Observational Study: baseline characteristics of participants and reliability of baseline measures. *Ann Epidemiol* **13:** S107 – S121

Larsson SC, Orsini N, Wolk A (2007) Body mass index and pancreatic cancer risk: a meta-analysis of prospective studies. *Int J Cancer* **120:** 1993 – 1998

Larsson SC, Permert J, Hakansson N, Naslund I, Bergkvist L, Wolk A (2005) Overall obesity, abdominal adiposity, diabetes and cigarette smoking in relation to the risk of pancreatic cancer in two Swedish population-based cohorts. *Br J Cancer* **93:** 1310 – 1315

Lin Y, Kikuchi S, Tamakoshi A, Yagyu K, Obata Y, Inaba Y, Kurosawa M, Kawamura T, Motohashi Y, Ishibashi T, JACC Study Group (2007) Obesity, physical activity and the risk of pancreatic cancer in a large Japanese cohort. *Int J Cancer* **120**(12)**:** 2665 – 2671

Lowenfels AB, Maisonneuve P, Lankisch PG (1999) Chronic pancreatitis and other risk factors for pancreatic cancer. *Gastroenterol Clin North Am* **28:** 673 – 685, x

Michaud DS, Giovannucci E, Willett WC, Colditz GA, Stampfer MJ, Fuchs CS (2001) Physical activity, obesity, height, and the risk of pancreatic cancer. *JAMA* **286:** 921 – 929

Nilsen TI, Vatten LJ (2000) A prospective study of lifestyle factors and the risk of pancreatic cancer in Nord-Trondelag, Norway. *Cancer Causes Control* **11:** 645 – 652

Nothlings U, Wilkens LR, Murphy SP, Hankin JH, Henderson BE, Kolonel LN (2007) Body mass index and physical activity as risk factors for pancreatic cancer: the Multiethnic Cohort Study. *Cancer Causes Control* **18:** 165 – 175

Pan SY, Johnson KC, Ugnat AM, Wen SW, Mao Y (2004) Association of obesity and cancer risk in Canada. *Am J Epidemiol* **159:** 259 – 268

Patel AV, Rodriguez C, Bernstein L, Chao A, Thun MJ, Calle EE (2005) Obesity, recreational physical activity, and risk of pancreatic cancer in a large US cohort. *Cancer Epidemiol Biomarkers Prev* **14:** 459 – 466

Pour PM, Kazakoff K, Carlson K (1990) Inhibition of streptozotocin-induced islet cell tumors and *N*-nitrosobis(2-oxopropyl)amine-induced pancreatic exocrine tumors in Syrian hamsters by exogenous insulin. *Cancer Res* **50:** 1634 – 1639

Pour PM, Stepan K (1984) Modification of pancreatic carcinogenesis in the hamster model. VIII. Inhibitory effect of exogenous insulin. *J Natl Cancer Inst* **72:** 1205 – 1208

Rapp K, Schroeder J, Klenk J, Stoehr S, Ulmer H, Concin H, Diem G, Oberaigner W, Weiland SK (2005) Obesity and incidence of cancer: a large cohort study of over 145 000 adults in Austria. *Br J Cancer* **93:** 1062 – 1067

Ritenbaugh C, Patterson RE, Chlebowski RT, Caan B, Fels-Tinker L, Howard B, Ockene J (2003) The Women's Health Initiative dietary modification trial: overview and baseline characteristics of participants. *Ann Epidemiol* **13:** S87 – S97

Schneider MB, Matsuzaki H, Haorah J, Ulrich A, Standop J, Ding XZ, Adrian TE, Pour PM (2001) Prevention of pancreatic cancer induction in hamsters by metformin. *Gastroenterology* **120:** 1263 – 1270

Sierra-Johnson J, Johnson BD, Bailey KR, Turner ST (2004) Relationships between insulin sensitivity and measures of body fat in asymptomatic men and women. *Obes Res* **12:** 2070 – 2077

Sinner PJ, Schmitz KH, Anderson KE, Folsom AR (2005) Lack of association of physical activity and obesity with incident pancreatic cancer in elderly women. *Cancer Epidemiol Biomarkers Prev* **14:** 1571 – 1573

Stefanick ML, Cochrane BB, Hsia J, Barad DH, Liu JH, Johnson SR (2003) The Women's Health Initiative postmenopausal hormone trials: overview and baseline characteristics of participants. *Ann Epidemiol* **13:** S78 – S86

Stolzenberg-Solomon RZ, Graubard BI, Chari S, Limburg P, Taylor PR, Virtamo J, Albanes D (2005) Insulin, glucose, insulin resistance, and pancreatic cancer in male smokers. *JAMA* **294:** 2872 – 2878

Tanko LB, Bruun JM, Alexandersen P, Bagger YZ, Richelsen B, Christiansen C, Larsen PJ (2004) Novel associations between bioavailable estradiol and adipokines in elderly women with different phenotypes of obesity: implications for atherogenesis. *Circulation* **110:** 2246 – 2252

Van Pelt RE, Evans EM, Schechtman KB, Ehsani AA, Kohrt WM (2001) Waist circumference vs body mass index for prediction of disease risk in postmenopausal women. *Int J Obes Relat Metab Disord* **25:** 1183 – 1188

Wang F, Herrington M, Larsson J, Permert J (2003) The relationship between diabetes and pancreatic cancer. *Mol Cancer* **2:** 4

Wolk A, Gridley G, Svensson M, Nyren O, McLaughlin JK, Fraumeni JF, Adam HO (2001) A prospective study of obesity and cancer risk (Sweden). *Cancer Causes Control* **12:** 13 – 21

Appendix

SHORT LIST OF WHI INVESTIGATORS

Programme Office: (National Heart, Lung, and Blood Institute, Bethesda, MD, USA) Elizabeth Nabel, Jacques Rossouw, Shari Ludlam, Linda Pottern, Joan McGowan, Leslie Ford, and Nancy Geller.

Clinical Coordinating Center: (Fred Hutchinson Cancer Research Center, Seattle, WA, USA)

Ross Prentice, Garnet Anderson, Andrea LaCroix, Charles L Kooperberg, Ruth E Patterson, Anne McTiernan; (Wake Forest University School of Medicine, Winston-Salem, NC, USA) Sally Shumaker; (Medical Research Labs, Highland Heights, KY, USA) Evan Stein; (University of California at San Francisco, San Francisco, CA, USA) Steven Cummings.

Clinical Centers: (Albert Einstein College of Medicine, Bronx, NY, USA) Sylvia Wassertheil-Smoller; (Baylor College of Medicine, Houston, TX, USA) Aleksandar Rajkovic; (Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA) JoAnn Manson; (Brown University, Providence, RI, USA) Annlouise R. Assaf; (Emory University, Atlanta, GA, USA) Lawrence Phillips; (Fred Hutchinson Cancer Research Centre, Seattle, WA, USA) Shirley Beresford; (George Washington University Medical Center, Washington, DC, USA) Judith Hsia; (Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA, USA) Rowan Chlebowski; (Kaiser Permanente Center for Health Research, Portland, OR, USA) Evelyn Whitlock; (Kaiser Permanente Division of Research, Oakland, CA, USA) Bette Caan; (Medical College of Wisconsin, Milwaukee, WI, USA) Jane Morley Kotchen; (MedStar Research Institute/Howard University, Washington, DC, USA) Barbara V Howard; (Northwestern University, Chicago/Evanston, IL, USA) Linda Van Horn; (Rush Medical Center, Chicago, IL, USA) Henry Black; (Stanford Prevention Research Center, Stanford, CA, USA) Marcia L Stefanick; (State University of New York at Stony Brook, Stony Brook, NY, USA) Dorothy Lane; (The Ohio State University, Columbus, OH, USA) Rebecca Jackson; (University of Alabama at Birmingham, Birmingham, AL, USA) Cora E Lewis; (University of Arizona, Tucson/Phoenix, AZ, USA) Tamsen Bassford; (University at Buffalo, Buffalo, NY, USA) Jean Wactawski-Wende; (University of California at Davis, Sacramento, CA, USA) John Robbins; (University of California at Irvine, CA, USA) F Allan Hubbell; (University of California at Los Angeles, Los Angeles, CA, USA) Howard Judd; (University of California at San Diego, LaJolla/Chula Vista, CA, USA) Robert D Langer; (University of Cincinnati, Cincinnati, OH, USA) Margery Gass; (University of Florida, Gainesville/Jacksonville, FL, USA) Marian Limacher; (University of Hawaii, Honolulu, HI, USA) David Curb; (University of Iowa, Iowa City/Davenport, IA, USA) Robert Wallace; (University of Massachusetts/Fallon Clinic, Worcester, MA, USA) Judith Ockene; (University of Medicine and Dentistry of New Jersey, Newark, NJ, USA) Norman Lasser; (University of Miami, Miami, FL, USA) Mary Jo O'Sullivan; (University of Minnesota, Minneapolis, MN) Karen Margolis; (University of Nevada, Reno, NV, USA) Robert Brunner; (University of North Carolina, Chapel Hill, NC, USA) Gerardo Heiss; (University of Pittsburgh, Pittsburgh, PA, USA) Lewis Kuller; (University of Tennessee, Memphis, TN, USA) Karen C Johnson; (University of Texas Health Science Center, San Antonio, TX, USA) Robert Brzyski; (University of Wisconsin, Madison, WI, USA) Gloria E Sarto; (Wake Forest University School of Medicine, Winston-Salem, NC, USA) Denise Bonds; (Wayne State University School of Medicine/Hutzel Hospital, Detroit, MI, USA) Susan Hendrix.