Cancer Causes and Control **12**: 13–21, 2001.

A prospective study of obesity and cancer risk (Sweden)

Alicja Wolk[1,*], Gloria Gridley[2], Malin Svensson[1], Olof Nyrén[1], Joseph K. McLaughlin[3], Joseph F. Fraumeni, Jr[2] & Hans-Olov Adami[1,4]
[1]*Karolinska Institutet, Department of Medical Epidemiology, Box 281, SE-171 77 Stockholm, Sweden; Ph: +46-8-728 6170; Fax: +46-8-31 49 57; E-mail: Alicja.Wolk@mep.ki.se;* [2]*Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA;* [3]*International Epidemiology Institute Ltd., Rockville, MD, USA;* [4]*Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA (*Author for correspondence)*

Received 20 February 2000; accepted in revised form 7 August 2000

Key words: cohort, neoplasms, obesity.

Abstract

Objective: We evaluated the relation between obesity and the risks for various forms of cancer.
Methods: In a population-based cohort of 28,129 hospital patients (8165 men, 19,964 women) with any discharge diagnosis of obesity (9557 only diagnosis, 5266 primary, 13,306 secondary) during 1965–1993, cancer incidence was ascertained through 1993 by record linkage to the nationwide Swedish Cancer Registry. Cancer risk was estimated using the standardized incidence ratio (SIR, with 95% confidence interval), which is the ratio of the observed number of cancers to that expected.
Results: Overall, a 33% excess incidence of cancer was seen in obese persons, 25% in men and 37% in women. Significant risk elevations were observed for cancers of the small intestine (SIR = 2.8; 95% CI 1.6–4.5), colon (1.3; 1.1–1.5), gallbladder (1.6; 1.1–2.3), pancreas (1.5; 1.1–1.9), larynx (2.1; 1.1–3.5), renal parenchyma (2.3; 1.8–2.8), bladder (1.2; 1.0–1.6), cervix uteri (1.4; 1.1–1.9), endometrium (2.9; 2.5–3.4), ovary (1.2; 1.1–1.5), brain (1.5; 1.2–1.9), and connective tissue (1.9; 1.1–3.0), and for lymphomas (1.4; 1.0–1.7), with higher risk observed for Hodgkin's disease only in men (3.3; 1.4–6.5) and for non-Hodgkin's lymphoma only in women (1.6; 1.2–2.1). The association of obesity with risk of breast, prostate and pancreas cancers was modified by age.
Conclusions: Obesity is associated with more forms of cancer than previously reported.

Introduction

Because obesity is increasingly common among economically developed populations its associated morbidity deserves careful study. With prevalence rates approaching or exceeding 30% among older age groups in Europe and the United States [1–3], obesity has become a major public health problem in developed countries. Around the world the prevalence of obesity has increased over time and appears to affect all age groups, including children [4].

It is well documented that obesity predisposes to diabetes, cardiovascular disease, and various digestive and musculoskeletal disorders, and a positive association has been reported between increasing body mass index and overall mortality [5–8]. In contrast, the risks of site-specific cancers associated with obesity are less well established. Although numerous case–control and cohort studies have investigated the relation of relative body weight with selected major cancers [9], there have been few long-term studies of cancer incidence or mortality overall and by cancer site [5, 10, 11]. Indeed, for some forms of cancer the relation to obesity has not been adequately assessed.

Our aim was to study risk of total and site-specific incident cancers in relation to obesity by comparing cancer incidence in a large Swedish cohort of hospitalized patients with a discharge diagnosis of obesity and with virtually complete follow-up extending up to 29 years, with cancer incidence in the general Swedish population.

Patients and methods

Study cohort

In Sweden there is virtually no private inpatient treatment, thus hospital-provided medical services are population-based and referable to the county in which the patient lives. In 1964–1965 the National Board of Health and Welfare started collecting data on individual hospital discharges in the Inpatient Register. In addition to national registration numbers (unique personal identifiers assigned to all Swedish residents), each record contains administrative and medical data such as hospital department and up to eight discharge diagnoses. The diagnoses are coded according to the seventh revision of the *International Classification of Diseases* (ICD7) through 1968, the eight revisions until 1987, and the ninth revision thereafter. The number of hospitals delivering data to the register has increased steadily: the register covered 60% of the Swedish population in 1969, 75% in 1978, and 85% by the end of 1983 [12]. From 1987 the register attained complete nationwide coverage.

All patients recorded in the Inpatient Register with a discharge diagnosis of obesity (ICD7 = 287.00, 287.09; ICD8 = 277.99; ICD9 = 278A) were initially selected for inclusion in the study. A total of 36,159 unique IDs were registered at least once with a diagnosis of obesity between 1965 and 1993.

Validity of obesity diagnosis

To facilitate generalization of our findings we evaluated the validity of the register data using 239 patients randomly selected from the obesity cohort. The hospital records for these patients were reviewed for data on height, weight, and concomitant discharge diagnoses at the time of the first in-hospital diagnosis of obesity. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Mean ($\pm$SD) and median of BMI was used to characterize the patients. As a measure of validity of the obesity diagnosis we calculated the positive predictive value. For men, according to the FAO/WHO/UNU Expert Consultation [13], a BMI higher than 30.0 kg/m^2 and for women BMI higher than 28.6 kg/m^2 were classified as obese; the corresponding values for overweight are 25.0 kg/m^2 and 23.8 kg/m^2.

Medical records were retrieved for 221 (92.5%) of 239 patients (155 in referral hospitals, 66 in local hospitals). At the time of the first obesity diagnosis, information on height and weight was available for a total of 165 patients, 86% of the men and 74% of the women. Table 1 presents BMI values by age for adult (>18 years) men and women. In the study sample, 15% of the men and 5% of the women had BMI values lower than the cutpoint for obesity, *i.e.* the positive predictive value of obesity diagnosis in our study was 85% in men and 95% in women. However, all patients were overweight. We found no important differences in BMI between cases in which obesity was the single diagnosis or the first of several diagnoses. The median BMI was 35.3 kg/m^2 (range 27.5–50.8) among men assigned their first obesity diagnosis at departments of internal medicine, 38.1 kg/m^2 (31.4–42.4) at surgical departments, and 32.8 kg/m^2 (27.1–43.0) at a specialized obesity unit. For women the corresponding median BMIs were 36.1 kg/m^2 (range 24.1–48.8), 36.1 kg/m^2 (27.3–44.8), and 35.1 kg/m^2 (30.1–48.4). Table 1 also shows the most frequent accompanying diagnoses at first hospitalization in relation to the BMI values. Among 17.1% of the men and 28.9% of the women there was no concomitant hospital diagnosis.

Table 1. Body mass index (BMI) and positive predictive value (PPV) of obesity as a discharge diagnosis, by gender and age in a sample of 165 patients from the Swedish Inpatient Register

	BMI (kg/m^2)					PPV (%)
	n	Median	Min–Max	Mean	95% CI	
Age groups (years)						
Men						
18–34	20	34.8	29.4–49.6	35.6	33.3–37.9	90
35–54	31	35.1	27.5–43.5	35.3	33.8–36.8	90
55–	31	31.8	27.1–50.8	33.7	31.8–35.6	77
All ages	82	33.7	27.1–50.8	34.8	33.7–35.8	85
Women						
18–34	19	34.9	24.1–42.3	34.9	33.1–36.7	95
35–54	35	35.9	25.6–48.8	36.9	34.9–38.8	94
55–	29	35.9	27.3–48.8	36.4	34.4–38.3	97
All ages	83	35.3	24.1–48.8	36.3	35.2–37.3	95
Concomitant diagnoses						
Men						
Hyperlipidemia	20	31.7	27.5–37.9	32.2	30.8–33.5	75
Diabetes	17	32.8	29.1–49.6	34.6	32.1–37.1	88
Hypertension	15	35.6	28.5–43.0	35.1	33.2–36.9	93
None	14	35.8	29.4–42.0	35.8	33.6–38.0	93
Women						
None	24	34.6	24.1–46.8	34.3	32.2–36.3	88
Hypertension	9	41.5	33.1–48.4	40.0	36.0–43.9	100
Diabetes	7	35.0	27.3–39.4	34.7	31.8–37.6	86
Osteoarthritis	7	34.2	33.7–47.0	36.2	32.6–39.8	100

Follow-up

Record linkage of the study cohort to the nationwide Register of Causes of Death allowed us to identify information on date of death among those deceased

through 1993. Corresponding linkage to the Migration Register identified dates of emigration. The National Swedish Cancer Register, founded in 1958 and close to 98% complete [14], was used to ascertain all incident cancers from the start of follow-up until 31 December 1993. The Cancer Register coded malignant neoplasms according to the ICD7 classification during the entire period of study.

To remove records with incorrect national registration numbers, which would otherwise contribute person-years at no risk of cancer, we also linked the cohort file to the Register of the Total Population. If a national registration number could not be found in this register, or in the reports of death and emigration, we concluded that it did not correspond to an existing person. We thus excluded from the cohort 4799 records because of erroneous or incomplete national registration numbers or inconsistencies uncovered during record linkage. We also excluded 1013 patients with prevalent cancers as well as 200 patients with cancers that occurred in the first year of follow-up (30,347 person-years) in order to minimize the possible impact of selection and detection biases. Such biases would occur if obese patients entered the cohort because of subclinical cancer and were diagnosed with cancer within 1 year, or if they received a cancer diagnosis because of hospital workup. The proportion of all cancers reported to the Cancer Register that were first detected at autopsy was about 8% in 1980 and 3.5% in 1993 [15]. The corresponding proportion in the obesity cohort was 8%. Because differences in autopsy rates between hospitalized patients with obesity and the general population might bias the risk estimates, we excluded from the cohort 127 cancers diagnosed after death. Thus, a total of 28,129 patients were entered into the study cohort, which is further characterized in Table 2.

Table 2. Characteristics of the obesity cohort in the Swedish Inpatient Register 1965–1993 followed-up during 1–29 years through 1993

Characteristics	Men	Women	All
No. of patients	8165	19,964	28,129
Mean age at entry, years	44.9	46.6	46.1
Mean calender year at entry	1980.0	1979.7	1979.8
Years of follow-up, mean	9.7	10.6	10.3
Person-years at risk	77,366.9	205,969.6	283,337
Obesity diagnosis at entry			
Only	2108	7449	9557
Primary	1540	3726	5266
Secondary	4517	8789	13,306
Mean age at the first cancer diagnosis, years	65.3	64.6	64.8

Statistical analysis

Follow-up time (person-years) was calculated from the date of entry into the cohort (date of the first hospital obesity diagnosis) until the occurrence of a first cancer diagnosis, emigration, death, or the end of the observation period (31 December 1993). The expected number of cancers was calculated by multiplying the number of person-years in each age-, gender, and calendar year category by age (in 5-year groups), sex, and calendar year-specific cancer incidence rates (excluding incidental cancers discovered at autopsy) derived from the entire Swedish population.

Certain diseases may be associated both with obesity and with elevated risk of some cancers. A higher prevalence of such conditions in the obesity cohort than in the general population would exaggerate our estimates of a relation between obesity and cancer. Therefore, in separate analyses we stratified the patients as to whether they had obesity as the only discharge diagnosis or as one of several primary or secondary diagnoses. Furthermore, because of findings from an earlier Scandinavian study [11], we performed stratified analyses of patients with and without diagnoses of alcoholism or liver cirrhosis with alcoholism. Since diabetes may be an intermediate step in the causal pathway linking obesity to certain cancers [16], we also performed separate analyses for those with and without reported hospital diagnosis of diabetes, to obtain a more valid estimate of the excess risk associated with obesity *per se*. We did not have any information from outpatient clinics concerning diabetes diagnoses. In the stratified analyses, person-years were allocated to the stratum without alcoholism/diabetes until a subject received a discharge diagnosis of alcoholism or diabetes.

Cancer risk was estimated as the standardized incidence ratio (SIR), defined as the ratio of the observed number of cancers to that expected. The 95% confidence interval (CI) of the SIR was calculated on the assumption that the observed number follows a Poisson distribution [17]. We used a chi-square statistic to test for trends of SIRs that appeared to be monotonically increasing or decreasing through age category [18].

Results

The study cohort, characterized in Table 2, comprised 8165 men and 19,964 women. A total of 1977 cancers occurred during 1–29 years of follow-up covering 283,337 person-years at risk.

The risks for cancer sites with at least 10 observed cases are presented in Table 3. Overall there was a 33%

Table 3. Standardized incidence ratios (SIR) with 95% confidence interval (CI) by sex for major cancer types during 1–29 years of follow-up among patients with obesity (only first cancers were counted and autopsy-incidental cancers were excluded)

Cancer site (ICD7-code)	Men			Women			All		
	Observed	SIR	95% CI	Observed	SIR	95% CI	Observed	SIR	95% CI
All cancer (140–209)	500	1.25	1.14–1.36	1477	1.37	1.30–1.44	1977	1.33	1.28–1.39
Buccal (140–148)	13	1.1	0.6–1.9	13	0.9	0.5–1.6	26	1.0	0.7–1.5
Stomach (151)	19	0.8	0.5–1.3	40	1.1	0.8–1.4	59	1.0	0.7–1.3
Small intestine (152)	9	4.0	2.2–9.3	8	1.9	0.8–3.7	17[a]	2.8	1.6–4.5
Colon (153)	33	1.2	0.8–1.6	109	1.3	1.1–1.6	142	1.3	1.1–1.5
Rectum (154)	30	1.5	1.0–2.1	44	1.0	0.7–1.4	74	1.2	0.9–1.4
Liver (155.0)	15	3.6	2.0–6.0	13	1.7	0.9–2.9	28	2.4	1.6–3.4
Gallbladder (155.1)	2	0.9	0.1–3.4	29	1.7	1.1–2.5	31	1.6	1.1–2.3
Extrahepatic bile ducts (155.2)	3	2.6	0.5–7.6	7	1.7	0.7–3.4	10	1.9	0.9–3.4
Pancreas (157)	29	2.4	1.6–3.4	34	1.1	0.8–1.5	63	1.5	1.1–1.9
Larynx (161)	9	1.9	0.9–3.6	4	2.5	0.7–6.4	13	2.1	1.1–3.5
Lung (162)	43	1.0	0.7–1.4	51	1.2	0.9–1.6	94	1.1	0.9–1.4
Breast (170)	2	3.0	0.3–10.9	309	1.1	0.9–1.2	311	1.1	1.0–1.2
Cervix uteri (171)	–	–	–	51	1.4	1.1–1.9	–	–	–
Endometrium (172)	–	–	–	189	2.9	2.5–3.4	–	–	–
Ovary (175)	–	–	–	77	1.2	1.1–1.5	–	–	–
Prostate (177)	93	1.0	0.8–1.3	–	–	–	–	–	–
Renal parenchyma (180.0)	25	2.0	1.3–3.0	55	2.4	1.8–3.2	80	2.3	1.8–2.8
Bladder (181)	32	1.1	0.8–1.6	35	1.4	1.0–1.9	67	1.2	1.0–1.6
Melanoma (190)	14	1.1	0.6–1.9	25	0.7	0.5–1.1	39	0.8	0.6–1.1
Nonmelanoma (191)	18	1.2	0.7–1.9	27	1.0	0.7–1.5	45	1.1	0.8–1.5
Brain (193)	19	1.6	1.0–2.5	47	1.5	1.1–1.9	66	1.5	1.2–1.9
Thyroid (194)	3	1.5	0.3–4.5	15	1.1	0.6–1.9	18	1.2	0.7–1.9
Connective tissue (197)	4	1.4	0.4–3.6	14	2.1	1.1–3.5	18	1.9	1.1–3.0
NHL (200 + 202)	9	0.7	0.3–1.3	43	1.6	1.2–2.1	52	1.3	1.0–1.7
Hodgkin's disease (201)	8	3.3	1.4–6.5	4	0.9	0.3–2.4	12	1.8	0.9–3.1
Multiple myeloma (203)	6	0.9	0.3–2.0	16	1.1	0.6–1.8	22	1.1	0.7–1.6
All leukemia (204)	15	1.4	0.8–2.3	24	1.2	0.7–1.7	39	1.2	0.9–1.7

[a] Eight adenocarcinoma, seven carcinoid, two leiomyosarcoma of the small intestine.

excess cancer incidence among obese persons, 25% among men and 37% among women. For men and women combined, significant risk elevations were observed for cancers of the colon (SIR = 1.3), larynx (SIR = 2.1), brain (SIR = 1.5), and renal parenchyma (SIR = 2.3). There was an excess risk of all lymphomas combined (ICD7 code 200–202, SIR = 1.4; 95% CI 1.0–1.7).

Some cancer sites showed differences in risk between men and women. Only men had significantly increased risks for cancers of the small intestine (SIR = 4.9), liver (SIR = 3.6), and pancreas (SIR = 2.4), and for Hodgkin's disease (SIR = 3.3). Only women showed significantly increased risks for cancers of the gallbladder (SIR = 1.7), urinary bladder (SIR = 1.4), and connective tissue (SIR = 2.1), and for non-Hodgkin's lymphoma (NHL) (SIR = 1.6). However, with the exception for pancreas cancer, none of the gender differences in risk was statistically significant. Cancers of the female reproductive organs were associated with obesity, with significant excess risks for the endometrium (SIR = 2.9), cervix (SIR = 1.4) and ovary (SIR = 1.2).

Stratified analyses

To assess possible confounding of cancer risk estimates by concomitant diseases in the cohort, we analyzed separately those patients with obesity as the only discharge diagnosis on entry to the cohort. A total of 361 cancers occurred in this subcohort of 9557 patients during 1–29 years of follow-up, with 99,829 person-years of observation. The overall cancer risk was only slightly lower in this subcohort of obese men and women (SIR = 1.25; 95% CI 1.1–1.4) than for the entire cohort.

A diagnosis of alcoholism (with or without cirrhosis) was recorded among 1582 patients in the obesity cohort (11.6% of men and 3.2% of women). We estimated risks separately in strata with never/ever recorded diagnosis of alcoholism. Those with a diagnosis of alcoholism

experienced significantly higher risks for all cancers combined, and for cancers of the liver and pancreas, than those without this diagnosis (confidence intervals not overlapping between those two subgroups) (Table 4). No overall excess risk for breast cancer was seen in either of these subcohorts.

In the obesity cohort 7193 patients (30.6% of the men and 23.5% of the women) had a diagnosis of diabetes. We studied risks in strata according to diabetes status as recorded in the hospital. Those with a diagnosis of diabetes had significantly higher risk for all cancers combined and for cancers of the liver and endometrium (Table 5). Only six of 28 patients with liver cancer had neither diabetes nor alcoholism/cirrhosis as co-diagnoses along with obesity.

Analysis by age at follow-up is presented in Table 6 for selected cancer sites. In obese women the incidence of breast cancer was lower than expected in younger women, and higher than expected in older women, who showed a significant trend with increasing age ($p = 0.0005$). In contrast, a significant decrease in the excess risk with advancing age was observed for cancers of the prostate ($p = 0.04$) and pancreas ($p < 0.0001$).

Discussion

This population-based Swedish cohort of hospitalized patients diagnosed with obesity was followed up for 29 years, an observation time longer than other cohort studies of obesity in the literature. Virtually all cohort members met standard diagnostic criteria, and obesity

Table 4. Standardized incidence ratios (SIR) with 95% confidence intervals (CI) for selected cancers during 1–29 years of follow-up by never/ever diagnosis of alcoholism with or without cirrhosis (autopsy-incidental cancers excluded)

Cancer site	No alcoholism, n = 26,547			Alcoholism, n = 1582		
	Observed	SIR	95% CI	Observed	SIR	95% CI
All cancer	1875	1.32	1.26–1.38	102	1.77	1.45–2.15
Small intestine	16	2.7	1.6–4.4	1	3.9	0.1–21.7
Colon	135	1.2	1.0–1.5	7	1.8	0.7–3.7
Liver	22	2.0	1.2–3.0	6	12.1	4.4–26.4
Gallbladder	31	1.7	1.1–2.4	0	0	0.0–8.0
Extrahepatic bile ducts	10	1.9	0.9–3.5	0	0	0.0–21.6
Pancreas	55	1.3	1.0–1.7	8	5.0	2.2–9.8
Larynx	12	2.1	1.1–3.6	1	2.1	0.0–11.6
Lung	88	1.1	0.9–1.4	6	1.2	0.5–2.7
Breast	303	1.1	0.9–1.2	8	1.2	0.5–2.4
Endometrium	184	2.9	2.5–3.4	5	3.6	1.2–8.4
Prostate	85	1.0	0.8–1.3	8	1.0	0.4–2.0
Brain	65	1.5	1.2–2.0	1	0.5	0.0–3.0

Table 5. Standardized incidence ratios (SIR) with 95% confidence intervals (CI) for selected cancer sites during 1–29 years of follow-up among obese patients without and with diabetes mellitus (autopsy-incidental cancers excluded)

Cancer site	No diabetes, n = 20,936			Diabetes, n = 7193		
	Observed	SIR	95% CI	Observed	SIR	95% CI
All cancer	1408	1.26	1.20–1.33	569	1.54	1.42–1.68
Small intestine	13	2.9	1.5–4.9	4	2.5	0.7–6.5
Colon	91	1.1	0.9–1.4	51	1.7	1.3–2.3
Liver	8	0.9	0.4–1.8	20	6.3	3.8–9.7
Gallbladder	24	1.7	1.1–2.5	7	1.4	0.6–3.0
Extrahepataic bile ducts	8	2.0	0.9–4.0	2	1.4	0.2–5.1
Pancreas	40	1.3	0.9–1.7	23	2.0	1.3–3.0
Breast	239	1.0	0.9–1.2	72	1.2	0.9–1.5
Endometrium	128	2.5	2.1–3.0	61	4.3	3.3–5.5
Prostate	56	0.9	0.7–1.2	37	1.2	0.8–1.6
Renal cell	55	2.1	1.6–2.8	25	2.7	1.8–4.0
Bladder	40	1.0	0.7–1.4	27	1.7	1.1–2.5
NHL	38	1.3	0.9–1.8	14	1.4	0.9–2.3

Table 6. Standardized incidence ratios (SIR) with 95% confidence interval (CI) for selected cancer sites by age at follow-up (cancer cases diagnosed during first year of follow-up and autopsy excluded)

Cancer site, by age, years	Observed	Expected	SIR	95% CI
Breast (female)				
≤49	36	52.99	0.7	0.5–0.9
50–59	56	65.39	0.9	0.6–1.1
60–69	108	83.73	1.3	1.1–1.6
70+	109	90.51	1.2	1.0–1.5
p-value for trend			0.0005	
Endometrium				
≤59	59	23.11	2.6	1.9–3.3
60–69	73	23.23	3.1	2.5–4.0
70+	57	18.47	3.1	2.3–4.0
p-value for trend			0.29	
Prostate				
≤59	9	6.03	1.5	0.7–2.8
60–69	34	32.26	1.1	0.7–1.5
70–74	27	22.75	1.2	0.8–1.7
74–79	18	17.55	1.0	0.6–1.6
80+	5	12.87	0.4	0.1–0.9
p-value for trend			0.04	
Pancreas				
≤59	19	7.50	2.5	1.5–4.0
60–69	28	14.32	2.0	1.3–2.8
70+	16	21.34	0.7	0.4–1.2
p-value for trend			<0.0001	
Renal cell				
<60	26	10.31	2.5	1.6–3.7
60–69	30	12.64	2.4	1.6–3.4
70+	24	12.08	2.0	1.3–3.0
p-value for trend			0.40	

was severe in many cases. Our results strongly support a positive association between obesity and the risks of several cancer sites. First, we quantified the excess risks previously established for cancers of the endometrium, renal parenchyma and gallbladder, and clarified the excess risks suspected for cancers of the colon, liver, pancreas, urinary bladder, cervix uteri, ovary, brain and Hodgkin's disease. Secondly, we found some new positive associations, notably with cancers of the small intestine, larynx, and with non-Hodgkin's lymphoma. Overall, we observed a 33% increased risk for all cancers; even after restricting the analysis to a subcohort of patients with obesity as the only diagnosis the overall excess cancer risk declined only slightly to 25%. Exclusion of patients with alcohol-related diagnoses had little effect on the overall cancer risk. However, when hospital-diagnosed diabetics were excluded the increased risk for liver cancer disappeared, while the risks for certain other cancers were attenuated. An excess risks of liver cancer in patients with diabetes has been reported previously, but control for body weight was not possible in that study [19].

Our study revealed an age-dependent effect of obesity on breast cancer risk, consistent with previous studies indicating a lowered risk in young women and an elevated risk after menopause [11, 20]. For prostate cancer there was no association overall, contrary to results of a recent large prospective study [21], but a positive relation was seen in cases diagnosed before age 60 and a negative relation after age 80. A similar age pattern was previously reported from a record-linkage cohort study in Denmark [11]. Also in agreement with the Danish obesity cohort, we observed a significant decline in risk for pancreas cancer with increasing age [11].

Our results provide further evidence for the established association between obesity and cancers of the endometrium [22], gallbladder [23], and renal parenchyma [24]. Although previous reports of renal cell cancer have indicated a stronger association among overweight women than men [24], our findings suggest that among clinically obese subjects the excess risk is similar in both sexes. We also found excess risks for colon cancer as reported in some but not all studies of this cancer [25]. In addition, we confirmed the excess risks for cancers of the liver, pancreas, and urinary bladder that were reported in a Danish obesity cohort with up to 11 years of follow-up [11]. The increased risk we observed for pancreas cancer is also consistent with two recent case–control studies [26, 27], although some earlier studies of this tumor found no association with obesity [28–30]. We also noted excess risks for cancers of the cervix uteri, ovary, brain and connective tissue, as reported in some earlier studies [9, 11, 31]. In contrast to the inverse associations reported in prospective studies between BMI and mortality due to stomach and lung cancers [5, 32, 33], we did not observe any unusual risks for these cancers, which agrees with results from the Danish study [11]. Furthermore, we did not observe an excess risk for thyroid cancer or multiple myeloma, in contrast to some earlier reports [34–36]. The increased risk of Hodgkin's disease associated with obesity in an earlier report [37] was confined to men in our study.

To our knowledge, increased risks associated with obesity have not been reported previously for cancers of the small intestine and larynx, and these need further evaluation. In a case–control study based on death certificates and information obtained from next of kin, no association was observed between BMI and cancers of the small intestine [38], while a recent hospital-based case–control study actually suggested an inverse relationship [39]. A significant association between obesity and non-Hodgkin's lymphoma was confined to women, in our study, and thus may indicate a chance finding.

Advantages of this study include its population-based character of hospitalized patients and – a relatively large number of cases for major forms of cancer as well as high positive predictive value of obesity diagnoses. Thus, underestimation of the excess risk due to misclassification of obesity is likely to be small. However, the reference population in our analyses of the standardized incidence ratios was the general adult Swedish population, not a population with normal weight, so that the true excess risks associated with obesity may be underestimated [40]. For comparison, in the 1980, the mean BMI in the general Swedish population aged 45–64 years, corresponding to our obesity cohort (mean age at entry 46 years and at cancer diagnosis 65 years), was 25.4 kg/m^2 among men [2] and 24.7 kg/m^2 among women [3]. Furthermore, the prevalence of obesity among Swedish men (BMI > 30 kg/m^2) was 9.8% [41] and among Swedish women (BMI > 28.6 kg/m^2) 19.9% [41].

Although we observed almost 2000 cancers overall, the number of subjects was small for many cancer sites, limiting the statistical power to detect some associations. In addition, because of the multiple comparisons performed, it is possible that some of our findings are due to chance. Another concern in linked-registry studies is the possibility of confounding by associated conditions such as alcoholism, diabetes or other unmeasured factors in a cohort of hospitalized subjects [42]. High alcohol consumption, as a source of extra calories, might contribute to obesity [43, 44], and alcohol is an independent etiologic factor for several cancer sites including the larynx [45], which showed an elevated risk in our study. In fact, the risks for all cancers combined,

and for liver and pancreatic cancers, tended to be higher in the subcohort of obese persons who also had a diagnosis of alcoholism. Because the overall cancer risk in the subcohort without associated diagnoses was only marginally lower than in the entire cohort, it is possible that some subjects in this group had unrecognized alcoholism or high alcohol consumption that might confound the results. On the other hand, a linked-registry study of alcoholics in Sweden found little evidence of elevated risks for obesity-related cancer sites [46]. Moreover, it should be noted that those subjects with diabetes that was mild or unrecognized, or that arose after entry to the cohort, might be prevalent in the subcohort without a recorded diagnosis of diabetes.

Several mechanisms may explain the association between obesity and the risk of various cancers, particularly those that may result from increased cell proliferation [47, 48]. In particular, obesity is associated with insulin resistance, compensatory hyperinsulinemia and increased growth factor production [49, 50], which in turn may stimulate mitogenesis and carcinogenesis [51–53]. The higher risks we observed for liver and pancreas cancers among men compared with women are paralleled by higher plasma insulin concentrations observed among obese men versus women [54, 55]. In fact, our results for liver cancer suggest that diabetes (or its treatment), along with alcoholism, account for the association with obesity.

An association between obesity and hormone-dependent cancers (*e.g.* breast, endometrium, prostate) seems biologically plausible. Among postmenopausal women the nearly-exclusive source of estrone is aromatization of plasma androstenedione in adipose tissue [56]. As a result, obese women have higher serum estrone and estradiol levels [57–59] and decreased levels of sex-hormone binding globulin (SHBG), leading to an increase in the amount of bioavailable estrogen [56, 60] that contributes to the risk of breast and endometrial cancer. Obese men also have lower levels of SHBG as well as testosterone [61]. In fact, the age-dependent effect of obesity on prostate cancer risk we observed is compatible with findings from a prospective study [62] suggesting that low levels of SHBG are a risk factor for prostate cancer in younger men, while low levels of testosterone are protective in older men. Other studies [63, 64] have also reported that the association of testosterone levels with subsequent risk of prostate cancer is greater among older men.

Obesity is also associated with several behaviors/lifestyles which may predispose to cancer. In particular, low physical activity is linked to obesity [43] and may contribute to the increased risks for colon cancer and possibly breast, endometrial, and prostate cancers [65–73]. Obese persons are also reported to consume more calories and fat, and less fibre [74], which may contribute to the risks of some cancers [45]. In addition, obese individuals tend to have lower blood levels of antioxidants [75, 76], perhaps due to lower consumption of fruits and vegetables that are considered protective for several cancer sites [45]. In Sweden, obese individuals also consume fewer vitamin supplements, including antioxidants such as vitamin C [80]. Moreover, obesity has been associated with decreased immune response [78, 79], which may contribute to the increased risks of lymphoma in our cohort.

In conclusion, this nationwide, population-based study of clinically obese patients indicated an excess risk of all cancers combined. We confirmed the established relation of obesity with endometrial, gallbladder, and renal cell cancers, and provided further evidence that the increased risk of breast cancer among obese women is restricted to postmenopausal women. Moreover, there was a positive association of obesity with cancers of the colon, pancreas, cervix uteri, ovary, urinary bladder, brain and connective tissue as reported in some previous studies. The excess risk we noted with liver cancer may be explained by concomitant diagnoses of diabetes and alcoholism. Not previously reported were the excess risks for cancers of the small intestine and larynx, and for Hodgkin's disease and non-Hodgkin's lymphomas. These associations deserve further investigation, as does the age-dependent effect of obesity on the risk of prostate and pancreas cancers.

Acknowledgements

We thank Shannon Keehn Merkle for her excellent computer support, and Monica Rundgren for secretarial assistance. This work was supported by grants from the National Cancer Institute (NO1-CP-85636) and from the Swedish Cancer Society.

References

1. Flegal KM, Carroll MD, Kuczmarski RJ, Johnson CL (1998) Overweight and obesity in the United States: prevalence and trends, 1960–1994. *Int J Obes Relat Metab Disord* **33**: 39–47.
2. Kuskowska-Wolk A, Bergström R (1993) Trends in body mass index and prevalence of obesity in Swedish men 1980–89. *J Epidemiol Commun Health* **47**: 103–108.
3. Kuskowska-Wolk A, Bergström R (1993) Trends in body mass index and prevalence of obesity in Swedish women 1980–89. *J Epidemiol Commun Health* **47**: 195–199.

4. Taubes G (1998) As obesity rates rise, experts struggle to explain why. *Science* **80**: 1367–1368.
5. Lew EA, Garfinkel L (1979) Variations in mortality by weight among 750,000 men and women. *J Chron Dis* **32**: 563–576.
6. Manson JE, Colditz GA, Stampler MJ, *et al*. (1990) A prospective study of obesity and risk of coronary heart disease in women. *N Engl J Med* **322**: 882–889.
7. Willett WC, Manson JE, Stampfer MJ, *et al*. (1995) Weight, weight change, and coronary heart disease in women. Risk within the ''normal'' weight range. *JAMA* **273**: 461–465.
8. Manson JE, Willett WC, Stampfer MJ, *et al*. (1995) Body weight and mortality among women. *N Engl J Med* **333**: 677–685.
9. Albanes D (1990) Energy balance, body size, and cancer. *Crit Rev Oncol Hematol* **10**: 283–303.
10. Whittemore AS, Paffenberger RS, Anderson K, Lee JE (1985) Early precursors of site-specific cancers in college men and women. *J Natl Cancer Inst* **74**: 43–51.
11. Möller H, Mellemgaard A, Lindvig K, Olsen JH (1994) Obesity and cancer risk: a Danish record-linkage study. *Eur J Cancer* **30A**: 344–350.
12. Nyrén O, McLaughlin JK, Gridley G, *et al*. (1995) Cancer risk after hip replacement with metal implants: a population-based cohort study in Sweden. *J Natl Cancer Inst* **87**: 28–32.
13. Joint FAO/WHO/UNU Export Consultation (1985) *Energy and Protein Requirements*. Geneva: WHO. Technical Report Series, No. **724**: 1–67.
14. Mattson B, Wallgren A (1984) Completeness of the Swedish Cancer Registry. *Acta Radiol* **23**: 305–313.
15. The Cancer Registry (1995) *Cancer Incidence in Sweden 1980* (*and 1993*) (annual publications). Stockholm: National Board of Health and Welfare.
16. Lindblad P, Chow WH, Chan J, *et al*. (1999) The role of diabetes mellitus in the aetiology of renal cell cancer. *Diabetologica* **42**: 107–112.
17. Bailar JC, Ederer F (1964) Significance factors for ratio of a Poisson variable to its expectation. *Biometrics* **20**: 639–643.
18. Breslow NE, Day NE (1987) The design and analysis of cohort studies. In: *Statistical methods in Cancer Research*, Vol. 2. IARC Scientific Publications No. 82. Lyon: International Agency for Research on Cancer.
19. Adami HO, Chow W-H, Nyrén O, *et al*. (1996) Excess risk of primary liver cancer in patients with diabetes mellitus. *J Natl Cancer Inst* **88**: 1472–1477.
20. Hunter DH, Willett WC (1996) Nutrition and breast cancer. *Cancer Causes Control* **7**: 56–68.
21. Andersson SO, Wolk A, Bergström R, *et al*. (1997) Body size and prostate cancer: a 20-year follow-up study among 135,006 Swedish construction workers. *J Natl Cancer Inst* **89**: 385-389.
22. Hill HA, Austin H (1996) Nutrition and endometrial cancer. *Cancer Causes Control* **7**: 19–32.
23. Fraumeni JF Jr, Devesa SS, McLaughlin JF, Stanford JL (1996) Biliary tract cancer. In: Schottenfield D, Fraumeni JJF, eds. *Cancer Epidemiology and Prevention*. Oxford: Oxford University Press, pp. 794–805.
24. Wolk A, Lindblad P, Adami HO (1996) Nutrition and renal cell cancer. *Cancer Causes Control* **7**: 5–18.
25. Potter JD (1999) Colorectal cancer: molecules and populations. *J Natl Cancer Inst* **91**: 916–932.
26. Ji BT, Hatch MC, Chow WH, *et al*. (1996) Anthropometric and reproductive factors and the risk of pancreatic cancer: a case–control study in Shanghai, China. *Int J Cancer* **66**: 32–37.
27. Silverman DT, Swanson CA, Gridley G, *et al*. (1998) Dietary and nutritional factors and pancreatic cancer: a case–control study based on direct interviews. *J Natl Cancer Inst* **90**: 1710–1719.
28. Mack TM, Yu MC, Hanish R, Henderson BE (1986) Pancreas cancer and smoking, beverage consumption, and past medical history. *J Natl Cancer Inst* **76**: 49–60.
29. Olsen GW, Mandel JS, Gibson RW, Wattenberg LW, Schuman LM (1991) Nutrients and pancreatic cancer: a population-based case–control study. *Cancer Causes Control* **2**: 291–297.
30. Howe GR, Ghadirian P, Bueno de Mesquita HB, *et al*. (1992) A collaborative case–control study of nutrient intake and pancreatic cancer within the SEARCH programme. *Int J Cancer* **51**: 365–372.
31. Zahm SH, Blair A, Holmes FF, Boysen CD, Robel RJ, Fraumeni JF Jr (1989) A case–control study of soft-tissue sarcoma. *Am J Epidemiol* **130**: 665-674.
32. Waaler HT (1984) Height, weight and mortality. The Norwegian experience. *Acta Med Scand* **Suppl. 1**: 679.
33. Nomura A, Heilbrun LK, Stemmermann GN (1985) Body mass index as a predictor of cancer in men. *J Natl Cancer Inst* **74**: 319.
34. Kolonel LN, Hankin JH, Wilkens LR, Fukunaga FH, Hinds MW (1990) An epidemiologic study of thyroid cancer in Hawaii. *Cancer Causes Control* **1**: 223–234.
35. Ron E, Kleinerman RA, Boice JD Jr, LiVolsi VA, Flannery JT, Fraumeni JF Jr (1987) A population-based case–control study of thyroid cancer. *J Natl Cancer Inst* **1**: 1–12.
36. Friedman GD, Herrinton LJ (1994) Obesity and multiple myeloma. *Cancer Causes Control* **5**: 479–483.
37. Paffenbarger RS Jr, Wing AL, Hyde RT (1977) Brief communication: Characteristics in youth indicative of adult-onset Hodgkin's disease. *J Natl Cancer Inst* **58**: 1489–1491.
38. Chow W-H, Linet MS, McLaughlin JK, Hsing AW, Co Chien HT, Blot WJ (1993) Risk factors for small intestine cancer. *Cancer Causes Control* **4**: 163–169.
39. Negri E, Bosetti C, La Vecchia C, Fioretti F, Conti E, Franceschi S (1999) Risk factors for adenocarcinoma of the small intestine. *Int J Cancer* **82**: 171–174.
40. Jones ME, Swerdlov AJ (1998) Bias in the standardized mortality ratio when using general population rates to estimate expected number of deaths. *Am J Epidemiol* **148**: 1012–1017.
41. Kuskowska-Wolk A, Rössner S (1992) Self-reported weight and height considerably affect the weight distribution of a population. Letter to the Editor. *Scand J Soc Med* **20**: 188–189.
42. Berkson J (1946) Limitations of the application of fourfold table analysis to hospital data. *Biomet Bull* **2**: 47–53.
43. Wolk A, Rössner S (1995) Effects of smoking and physical activity on body weight: development in Sweden between 1980 and 1989. *J Intern Med* **237**: 287–291.
44. Istvan J, Murray R, Voelker H (1995) The relationship between patterns of alcohol consumption and body weight. *Int J Epidemiol* **24**: 543–546.
45. Willett WC, Trichopoulos D (1996) Nutrition and cancer: a summary of the evidence. *Cancer Causes Control* **7**: 178–180.
46. Adami HO, McLaughlin JK, Hsing AW, *et al*. (1992) Alcoholism and cancer risk: a population-based cohort study. *Cancer Causes Control* **3**: 419–425.
47. Preston-Martin S, Pike MC, Ross RK, Jones PA, Henderson BE (1990) Increased cell division as a cause of human cancer. *Cancer Res* **50**: 7415–7421.
48. Farber E (1995) Cell proliferation as a major risk factor for cancer: a concept of doubtful validity. *Cancer Res* **55**: 3759–3762.

49. Flyvbjerg A, Orskov H (1990) Growth hormone, insulin-like growth factors and diabetes. In: Alberti KGMM, Krall LP, eds, *The Diabetes Annual 5*. Amsterdam: Elsevier, pp. 642–656.
50. Lorenzi M, Cagliero E (1991) Pathobiology of endothelial and other vascular cells in diabetes mellitus. *Diabetes* **40**: 653–659.
51. Kahn CR, White MF (1995) Molecular mechanism of insulin action. In: DeGroot LJ, ed. *Endocrinology*. Philadelphia: WB Saunders, pp. 1373–1388.
52. Russel WE, Van Wyk JJ (1995) Peptide growth factors. In: DeGroot LJ, ed. *Endocrinology*. Philadelphia: WB Saunders, pp. 2590–2623.
53. Tabor E (1994) Tumor suppressor genes, growth factor genes, and oncogenes in hepatitis B virus-associated hepatocellular carcinoma. *J Med Virol* **42**: 357–365.
54. McKeigue PM, Laws A, Chen YD, Marmot MG, Reaven GM (1993) Relation of plasma triglyceride and apo-B levels to insulin-mediated suppression of nonesterified fatty acids. *Arterioscler Thromb* **13**: 1187–1192.
55. Ferrara A, Barrett-Connor E, Wingard DL, Edelstein AL (1995) Sex differences in insulin level in older adults and the effect of body size, estrogen replacement therapy, and glucose tolerance status. *Diabetes Care* **18**: 220–225.
56. MacDonald PC, Siiteri PK (1974) The relationship between the extraglandular production of estrone and the occurrence of endometrial neoplasia. *Gynecol Oncol* **2**: 259–263.
57. Folsom AR, Kaye SA, Potter JD, Prineas RJ (1989) Association of incident carcinoma of the endometrium with body weight and fat distribution in older women: early findings of the Iowa Women's Health Study. *Cancer Res* **49**: 6828–6831.
58. Austin H, Austin JM Jr, Partridge EE, Hatch KD, Shingleton HM (1991) Endometrial cancer, obesity, and body fat distribution. *Cancer Res* **51**: 568–572.
59. Judd HL, Lucas WE, Yen SS (1976) Serum 17 beta-estradiol and estrone levels in postmenopausal women with and without endometrial cancer. *J Clin Endocrinol Metab* **43**: 272–278.
60. Davidson BJ, Gambone JC, Lagasse LD, *et al*. (1981) Free estradiol in postmenopausal women with and without endometrial cancer. *J Clin Endocrinol Metab* **52**: 404–408.
61. Field AE, Colditz GA, Willett WC, Longcope C, McKinley JB (1994). The relation of smoking, age, relative weight, and dietary intake to serum adrenal steroids, sex hormones, and sex hormone-binding globulin in middle-aged men. *J Clin Endocrinol Metab* **79**: 1310–1316.
62. Gann PH, Hennekens CH, Ma J, Longcope C, Stampfer MY (1996) A prospective study of sex hormone levels and risk of prostate cancer. *J Natl Cancer Inst* **88**: 1118–1126.
63. Hsing AW, Comstock GW (1993) Serological precursors of cancer: serum hormones and risk of subsequent prostate cancer. *Cancer Epidemiol Biomarkers Prev* **2**: 27–32.
64. Wolk A, Andersson SO, Bergström R (1997) Re: Prospective study of sex hormone levels and risk of prostate cancer. *J Natl Cancer Inst* **89**: 56.
65. Gerhardsson M, Floderus B, Norell S (1988) Physical activity and colon cancer risk. *Int J Epidemiol* **17**: 743–746.
66. Lee IM, Paffenbarger RS Jr, Hsieh CC (1992) Physical activity and risk of prostatic cancer among college alumni. *Am J Epidemiol* **135**: 169–179.
67. Hsing AW, McLaughlin JK, Zheng W, Gao YT, Blot WJ (1994) Occupation, physical activity and risk of prostate cancer in Shanghai, People's Republic of China. *Cancer Causes Control* **5**: 136–140.
68. Bernstein L, Henderson BE, Hanisch R, Sullivan-Hally J, Ross RK (1994) Physical exercise and reduced risk of breast cancer in young women. *J Natl Cancer Inst* **86**: 1403–1408.
69. Moradi T, Nyrén O, Bergström R, *et al*. (1998) Risk for endometrial cancer in relation to occupational physical activity; a nationwide cohort study in Sweden. *Int J Cancer* **76**: 665–670.
70. Andersson SO, Baron J, Wolk A, Lindgren C, Bergström R, Adami HO (1995) Early life risk factors for prostate cancer. A population-based case–control study in Sweden. *Cancer Epidemiol Biomarkers Prev* **4**: 187–192.
71. Longnecker MP, Gerhardsson de Verdier M, Frumkin H, Carpenter C (1995) A case–control study of physical activity in relation to risk of cancer of the right colon and rectum in men. *Int J Epidemiol* **24**: 42–50.
72. D'Avanzo B, Nanni O, LaVecchia C, *et al*. (1996) Physical activity and breast cancer risk. *Cancer Epidemiol Biomarkers Prev* **5**: 155–160.
73. Thune I, Lund E (1996) Physical activity and risk of colorectal cancer in men and women. *Br J Cancer* **73**: 1134–1140.
74. Drewnowski A, Kurth C, Holden-Wiltse J, Saari J (1992) Food preferences in human obesity: carbohydrates versus fats. *Appetite* **18**: 207–221.
75. Hotzel D (1986) Suboptimal nutritional status in obesity. *Bibl Nutr Dieta* **37**: 36–41.
76. Moor de Burgos A, Wartanowicz M, Ziemlanski S (1992) Blood vitamin and lipid levels in overweight and obese women. *Eur J Clin Nutr* **46**: 803–806.
77. Wolk A, Rössner S (1996) Obesity and self-perceived health in Sweden. *Int J Obes* **20**: 369–372.
78. Chandra RK (1997) Nutrition and the immune system: an introduction. *Am J Clin Nutr* **66**: 460S–463S.
79. Stallone DD (1994) The influence of obesity and its treatment on the immune system. *Nutr Rev* **52**: 37–50.