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Association of Obesity and Cancer Risk in Canada

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The authors conducted a population-based, case-control study of 21,022 incident cases of 19 types of cancer and 5,039 controls aged 20–76 years during 1994–1997 to examine the association between obesity and the risks of various cancers. Compared with people with a body mass index of less than 25 kg/m^2, obese (body mass index of ≥30 kg/m^2) men and women had an increased risk of overall cancer (multivariable adjusted odds ratio = 1.34, 95% confidence interval (CI): 1.22, 1.48), non-Hodgkin's lymphoma (odds ratio = 1.46, 95% CI: 1.24, 1.72), leukemia (odds ratio = 1.61, 95% CI: 1.32, 1.96), multiple myeloma (odds ratio = 2.06, 95% CI: 1.46, 2.89), and cancers of the kidney (odds ratio = 2.74, 95% CI: 2.30, 3.25), colon (odds ratio = 1.93, 95% CI: 1.61, 2.31), rectum (odds ratio = 1.65, 95% CI: 1.36, 2.00), pancreas (odds ratio = 1.51, 95% CI: 1.19, 1.92), breast (in postmenopausal women) (odds ratio = 1.66, 95% CI: 1.33, 2.06), ovary (odds ratio = 1.95, 95% CI: 1.44, 2.64), and prostate (odds ratio = 1.27, 95% CI: 1.09, 1.47). Overall, excess body mass accounted for 7.7% of all cancers in Canada—9.7% in men and 5.9% in women. This study provides further evidence that obesity increases the risk of overall cancer, non-Hodgkin's lymphoma, leukemia, multiple myeloma, and cancers of the kidney, colon, rectum, breast (in postmenopausal women), pancreas, ovary, and prostate.

body mass index; case-control studies; neoplasms; obesity

Abbreviations: CI, confidence interval; IGF, insulin-like growth factor; NECSS, National Enhanced Cancer Surveillance System.

The prevalence of obesity has reached epidemic levels over the last two decades, and obesity is now known to be a major contributor to the global burden of disease (1). The World Health Organization estimated that approximately 250 million people are now obese worldwide, and there will be 300 million obese people in 2025 (2). In 1999–2000, 33.5 percent of the adult population in the United States was overweight and about 30.5 percent was obese (3). About half of the adult population in Europe is overweight or obese (4). About 33 percent of adult Canadians are overweight and 15 percent are obese (5). Obesity prevalence is increasing rapidly, and obesity is becoming a problem even in urban areas of developing countries (6). Obesity is associated with several chronic diseases, including hypertension, type 2 diabetes, heart disease, stroke, some types of cancer, poor mental health, respiratory problems, and arthritis-related disability (1). More than 280,000 annual deaths are attributable to obesity among US adults (7). Obesity seems to reduce life expectancy markedly, especially among younger adults (8). Obesity-related health problems consume about 7 percent of the US health-care budget in direct medical costs (9) and about 1–5 percent in Europe (10). It is estimated that the total cost (direct and indirect) for obesity-related health problems is around $100 billion annually in the United States (11) and $1.8 billion (2.4 percent of total health-care expenditures for all diseases) in Canada (12).

Although the associations between obesity and diabetes, cardiovascular disease, and various digestive and musculoskeletal disorders are well documented, the relation of obesity to overall cancer and site-specific cancers has not

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been conclusively established. There is growing evidence that overweight and obesity are associated with some cancer sites, such as the kidney, breast (in postmenopausal women), colon, esophagus, and endometrium (13), but studies on the relation between obesity and overall cancer or other forms of cancers are sparse and the results are inconsistent (13). We therefore assessed the relation of obesity to overall cancer and site-specific cancers, using a large, population-based, case-control study in Canada, the National Enhanced Cancer Surveillance System (NECSS).

MATERIALS AND METHODS

Study population

The present study is based on data from subjects who participated in the NECSS, a collaborative project of Health Canada and the provincial cancer registries designed to provide a better understanding of the relation between environmental risk factors and cancer. The NECSS collected data from 21,022 Canadians with one of 19 types of cancer and 5,039 population controls between 1994 and 1997 in eight of the 10 Canadian provinces (Alberta, British Columbia, Manitoba, Newfoundland, Nova Scotia, Ontario, Prince Edward Island, and Saskatchewan).

The provincial cancer registries obtained approval of the study proposal from their respective ethics review boards. The registries identified 37,344 incident cases aged 20–76 years with histologically confirmed primary cancer, newly diagnosed between 1994 and 1997. Among these cases, 4,036 (10.8 percent) people died before they could be sent questionnaires. Physicians refused to give consent to contact 2,684 (7.1 percent) cases. Questionnaires were sent to 30,624 cases (1,476 questionnaires were returned because of wrong or old addresses, and no updated address could be found through publicly available sources), and 27,887 cases were contacted. In total, 21,022 people completed and returned questionnaires, representing 68.6 percent of the eligible subjects and 75.4 percent of those contacted.

The NECSS used frequency matching to the overall case group with similar age and sex distributions in the selection of population controls, so that there would be at least one control for every case within each sex and 5-year age group for any specific cancer site within each province. The sampling strategy for control selection varied by province depending on data availability, data quality (completeness and timeliness), and the confidentiality restrictions of provincial databases. In Ontario, the Provincial Ministry of Finance Property Assessment databases, which are intended to include all residents of the province and are updated monthly, were used to obtain a stratified random sample. Prince Edward Island, Nova Scotia, Manitoba, Saskatchewan, and British Columbia used provincial health insurance plans to get a random sample of the provincial population stratified by age group and sex. More than 95 percent of Canadians are covered by these public plans, and individuals are excluded only if they are covered through other federal plans. Newfoundland and Alberta used similar random digit dialing protocols to obtain population samples. In Alberta, the University of Alberta's Population Research Laboratory generated a random sample of provincial telephone numbers including unlisted numbers. Each randomly selected phone number was called up to eight times on a pattern structured around call attempts on one weekday during the day, four weekday evenings, and Saturday during the day. Of the numbers called, 4 percent were not in service or businesses, there was a communication barrier in 3.6 percent, and there was no answer after attempting to call eight times for 11.5 percent of numbers. Of those households contacted, 91.3 percent agreed to a census of residents, and 90.1 percent of the eligible individuals agreed to have a questionnaire sent. Ninety-nine percent of Albertan households have telephones, and the Laboratory estimates that between 92 percent and 97 percent of people in the province are reachable. The Newfoundland Telephone Company provided the local cancer registry with a random sample of Newfoundland phone numbers including unlisted numbers. Exact contact and eligibility rates are unavailable; however, study personnel estimated that 85 percent of phone numbers were reached. Cooperation levels were similar to those in Alberta. Of the controls who were sent questionnaires, 83 percent and 75 percent completed and returned questionnaires for Alberta and Newfoundland, respectively. The response rate for eligible cases was 64.0 percent for Alberta and 62.8 percent for Newfoundland.

The cancer registries mailed the same questionnaires used for cases to 8,117 subjects selected as potential controls, using the same protocol as for cases. Questionnaires were returned for 573 controls (7.4 percent) because of a wrong or old address, and no updated address could be found. A total of 5,039 controls completed and returned questionnaires, representing 62.1 percent of the ascertained controls and 66.8 percent of the eligible controls.

Data collection

A pilot questionnaire was tested in seven provinces in 1993, and then a revised version of the questionnaire was developed for the main study.

The cancer registries identified most cases within 1–3 months of diagnosis through pathology reports in order to reduce the loss of subjects caused by severe illness and death. The registries first obtained physicians' consent to approach cancer cases and then sent the patients a covering letter and questionnaire to complete and return in a stamped, preaddressed envelope. If the questionnaire was not completed and returned in time, a reminder postcard was sent out at 2 weeks, a second copy of the questionnaire was sent at 4 weeks, and telephone contact was attempted after 6 weeks to offer the subject a telephone interview, if desired. Telephone follow-up was attempted when necessary for clarification and completeness.

Each subject was assigned a reference date defined as 2 years before the interview. Information was collected on demographic factors, height, weight history, diet, smoking history, physical activity, alcohol consumption, vitamin and mineral supplements, employment history, residential history, and occupational exposure to specific carcinogens on or before the reference date. Information on menstrual,

reproductive, and mammography history was collected also for women.

Respondents were asked questions about their adult height, reference weight, and maximum lifetime weight (excluding weight during pregnancy). As a measure of overweight and obesity, body mass index was calculated as the reference weight in kilograms divided by height in meters squared. Based on World Health Organization standards, obesity was defined for both sexes as a body mass index of 30 kg/m^2 or more, and overweight was defined as a body mass index between 25 and less than 30 kg/m^2 (1).

The questionnaire gathered information on recreational physical activity before the reference date. The frequency and duration of activities were assessed by recording the session frequency, season participated, and average time per session for each of 12 of the most common types of moderate and strenuous leisure-time physical activity in Canada. Individual activities included walking for exercise, jogging or running, gardening or yard work, home exercise or exercise class, golf, racquet sports, bowling or curling, swimming or water exercise, skiing or skating, bicycling, social dancing, and other strenuous exercise. The intensity of the activity was estimated by assigning a specific metabolic equivalent value to each reported activity. The metabolic equivalent values used here were abstracted from the *Compendium of Physical Activities* (14). A metabolic equivalent is defined as the ratio of the associated metabolic rate for a specific activity to the resting metabolic rate (15). One metabolic equivalent is the average seated resting energy cost for an adult and is set at 3.5 ml of oxygen per kg per minute. The metabolic equivalent score of each activity was multiplied by the midpoint of the reported frequency of the activity, then converted to the frequency of activity per week, and summed to create a composite index of total recreational physical activity per week (16). The variable used in the analysis was the composite index of total recreational physical activity.

The questionnaire also collected information on diet from 2 years before the interview through the use of a 60-item food frequency instrument and general changes in the diet compared with 20 years ago. It was designed according to two instruments that have been extensively validated: the National Cancer Institute Block questionnaire (17) and the instrument used in the Nurses' Health Study cohort (18), with minor modification for the Canadian diet. We calculated the intake of total calories and total dietary fiber for each individual by substituting the number of kilojoules and grams of dietary fiber for each of the items in the diet questionnaire using the Canadian Nutrient Guide (19).

Statistical analysis

We estimated the risks of overall cancer and of site-specific cancers associated with obesity and overweight by odds ratios and 95 percent confidence intervals, using unconditional logistic regression modeling with the SAS version 8 software package (SAS Institute, Inc., Cary, North Carolina) and adjusting for potential confounders. Subjects were categorized according to their body mass index (<25, 25–<30, ≥30 kg/m^2). We conducted a full assessment of the potential confounders and effect modification in the initial regression models. We adjusted the final models for 5-year age groups, province of residence, educational level (≤9, 10–11, 12–13, ≥14 years), smoking (0, 1–9, 10–19, 20–29, 30–39, ≥40 pack-years), alcohol consumption (0, <2.1, 2.1–<7.5, ≥7.5 drinks per week), composite index of total recreational physical activity (frequencies/week, quartiles), total caloric intake (kilojoules per week, quartiles), total vegetable consumption (servings per week, quartiles), dietary fiber intake (grams per week, quartiles), and multivitamin intake (20-year frequency: no, not regularly, fairly regularly). For women, we also adjusted the models for menopausal status (yes, no), parity (0, 1, 2, 3, ≥4 births), age at menarche (<12, 12–13, 14–15, >15 years), and age at end of first pregnancy (<20, 20–23, 24–29, ≥30 years). Quartiles of variables were based on the frequency distribution of the control population.

We examined the possible effect modification by gender, cigarette smoking, and alcohol drinking, because these factors have been identified or suggested previously as possible effect modifiers in other studies (20–22), and several cancers are known to be related to smoking. We conducted tests for trend for all models of categorized data by treating the different categories as a single ordinal variable.

On the bases of the prevalence of overweight and obesity in the Canadian population determined by the latest Canadian Community Health Survey (5) and our estimated odds ratios, we calculated the population attributable risks and corresponding 95 percent confidence intervals of overall cancer and some specific cancers related to overweight and obesity using the methods derived by Walter (23). The calculation assumes that our odds ratio estimates associated with overweight and obesity were causal and generalizable to the Canadian population.

RESULTS

Table 1 compares the distribution of major characteristics among cases and controls. Cases tended to be older, less educated, and more often former smokers or current smokers; they had more pack-years of smoking; and they drank more alcohol and consumed more calories and fat than did controls of both sexes. Male cases also drank more alcohol than did male controls. Cases and controls were similar with regard to family income, total dietary fiber intake, and vegetable and fruit consumption.

Table 2 presents the odds ratios for overall cancer and site-specific cancers associated with excess body mass index. For overall cancer, overweight and obesity were associated, respectively, with odds ratios of 1.14 (95 percent confidence interval (CI): 1.04, 1.25) and 1.29 (95 percent CI: 1.13, 1.47) among men, 1.02 (95 percent CI: 0.92, 1.13) and 1.41 (95 percent CI: 1.22, 1.61) among women, and 1.09 (95 percent CI: 1.02, 1.17) and 1.34 (95 percent CI: 1.22, 1.48) among both sexes combined. An increased odds ratio was observed in obese people for non-Hodgkin's lymphoma, leukemia, multiple myeloma, and cancers of the kidney, colon, rectum, pancreas, breast (postmenopausal women), and ovary. In contrast, a decreased risk of lung cancer was observed in

TABLE 1. Characteristics of all cancer cases and controls (*n* = 26,061), National Enhanced Cancer Surveillance System, Canada, 1994–1997

Characteristic	Men			Women		
	Cases (*n* = 11,500)	Controls (*n* = 2,547)	*p* value	Cases (*n* = 9,522)	Controls (*n* = 2,492)	*p* value
Age (years) (mean (SD*))	60.0 (12.0)	57.7 (14.7)	<0.0001	58.3 (11.7)	55.8 (12.4)	<0.0001
Never smoked (%)	21	26.7		40.3	50.4	
Former smoker (%)	50.6	48.8		32.1	29.3	
Current smoker (%)	28.4	24.5		27.6	20.3	
Pack-years of smoking (mean (SD))	21.4 (21.4)	16.8 (19.5)	<0.0001	12.7 (16.7)	7.7 (12.8)	<0.0001
Alcohol drinking (servings/week) (mean (SD))	8.1 (12.7)	7.1 (11.4)	0.0003	2.8 (5.9)	2.6 (5.4)	0.39
Educational level (years) (mean (SD))	11.6 (3.9)	12.0 (4.1)	<0.0001	11.7 (3.4)	12.1 (3.5)	<0.0001
Low family income (%)	20.3	20.5		27.5	23.7	
Lower-middle family income (%)	23.2	22.6		22.9	23.4	
Upper-middle family income (%)	32.2	34.1		30.4	32.9	
High family income (%)	24.1	22.8		19.2	19.9	
Body mass index (kg/m^2) (mean (SD))	26.7 (4.6)	26.2 (4.2)	<0.0001	25.7 (5.4)	25.3 (5.3)	0.0001
Total calorie intake (kJ/week) (mean (SD))	56,613 (24,800)	54,154 (24,312)	<0.0001	48,853 (19,667)	48,362 (24,270)	0.29
Total fat intake (g/week) (mean (SD))	399.8 (226.8)	376.9 (213.3)	<0.0001	329.8 (169.3)	320.5 (234.1)	0.026
Vegetable consumption (servings/week) (mean (SD))	19.8 (14.4)	20.1 (13.8)	0.27	21.1 (14.1)	21.1 (14.8)	0.95
Fruit consumption (servings/week) (mean (SD))	10.5 (9.5)	10.5 (10.3)	0.82	11.9 (9.9)	12.1 (9.4)	0.41
Dietary fiber intake (g/week) (mean (SD))	137.3 (78.1)	141.2 (74.7)	0.019	139.1 (70.4)	139.7 (71.3)	0.73
Total recreational physical activity (frequencies/week) (mean (SD))	28.3 (27.6)	28.5 (27.3)	0.81	24.2 (23.4)	25.3 (22.7)	0.029

* SD, standard deviation.

men and women who were overweight or obese. However, we did not see any relation between overweight or obesity and risk of cancers of the liver, brain, or bone/cartilage for either sex; testicular cancer for men; or cancers of the breast (premenopausal), bladder, stomach, or salivary glands for women.

We also examined the relation of overall and site-specific cancers with obesity and overweight stratified by cigarette smoking (table 3). Smoking did not substantially modify the positive association of obesity with non-Hodgkin's lymphoma, leukemia, multiple myeloma, and cancers of the kidney, colon, ovary, and pancreas. However, the positive associations with obesity disappeared for overall cancer and cancers of the rectum, breast (in women), and prostate among obese current smokers and for salivary gland cancer among obese never smokers. For lung cancer, a decreased odds ratio was observed among obese current smokers and former smokers but not among obese never smokers.

When we looked at the association between cancers and obesity stratified by alcohol drinking (ever/never drank), we did not observe any increased risk associated with obesity for prostate cancer among those who ever drank alcohol or for cancers of the pancreas and stomach among those who never drank alcohol (data not shown). Alcohol drinking basically did not modify the associations between obesity and other cancers (data not shown).

We calculated the proportion of overall cancer and some specific cancers attributable to overweight and obesity (table 4). Overweight and obesity together accounted for 7.7 percent of overall cancer—9.7 percent for men and 5.9 percent for women. For specific cancers, the greatest portion attributable to overweight and obesity was for kidney cancer (41 percent), followed by colon cancer (23.9 percent), rectal cancer (19.5 percent), leukemia (17.7 percent), ovarian cancer (15.6 percent), postmenopausal breast cancer (12.5 percent), and non-Hodgkin's lymphoma (11.2 percent).

DISCUSSION

Our study found that obese and overweight people had respective risks of 34 percent and 9 percent higher for all 19 cancers combined compared with subjects with a body mass index of less than 25 kg/m^2. Obese people had an increased risk of non-Hodgkin's lymphoma, leukemia, multiple myeloma, and cancers of the kidney, colon, rectum, breast (in postmenopausal women), ovary, pancreas, and prostate. These observations provide strong evidence for the positive association between obesity and overall cancer and some site-specific cancers. If the association were causal, overweight and obesity would be responsible for 7.7 percent of overall cancer.

Our study has several strengths. First, the study population was based on eight provinces, so that selection bias was substantially reduced. Second, the large sample size allowed an assessment of the effect of obesity on overall cancer as well as on specific cancers, including some rare ones that have not been studied before. Finally, the ability to examine many cancers in the same study made it possible to compare the effect of obesity on different types of cancer. Results obtained from different studies are often difficult to reconcile because of differences in study design, implementation, population profile, data analysis, and interpretation.

TABLE 2. Risk of overall cancer and site-specific cancers associated with excess body mass index (kg/m^2), National Enhanced Cancer Surveillance System, Canada, 1994–1997

Cancer site (ICD-O/2* code; ICD-9* code)	Men†						Women†						All†					
	No. of cases	BMI*: 25–<30 (adjusted)‡		BMI: ≥30 (adjusted)‡		*p* for trend	No. of cases	BMI: 25–<30 (adjusted)§		BMI: ≥30 (adjusted)§		*p* for trend	No. of cases	BMI: 25–<30 (adjusted)¶		BMI: ≥30 (adjusted)¶		*p* for trend
		OR*	95% CI*	OR	95% CI			OR	95% CI	OR	95% CI			OR	95% CI	OR	95% CI	
All cancers	11,500	1.14	1.04, 1.25	1.29	1.13, 1.47	<0.0001	9,522	1.02	0.92, 1.13	1.41	1.22, 1.61	<0.0001	21,022	1.09	1.02, 1.17	1.34	1.22, 1.48	<0.0001
Kidney (C64; 189.0)	727	2.03	1.65, 2.50	3.15	2.45, 4.05	<0.0001	618	1.49	1.20, 1.85	2.42	1.89, 3.09	<0.0001	1,345	1.77	1.53, 2.05	2.74	2.30, 3.25	<0.0001
Colon (C18; 153)	959	1.54	1.27, 1.86	2.16	1.68, 2.78	<0.0001	768	1.22	0.98, 1.52	1.77	1.35, 2.32	<0.0001	1,727	1.40	1.21, 1.61	1.93	1.61, 2.31	<0.0001
Rectum (C19–C21; 154)	858	1.41	1.15, 1.71	1.75	1.35, 2.28	<0.0001	589	1.28	1.02, 1.61	1.50	1.11, 2.02	0.0045	1,447	1.36	1.17, 1.57	1.65	1.36, 2.00	<0.0001
Breast (C50; 174/175)	81	1.84	0.92, 3.67	1.86	1.09, 3.20	0.042	2,364	1.08	0.94, 1.24	1.51	1.26, 1.80	<0.0001	2,445	1.10	0.97, 1.26	1.47	1.24, 1.73	<0.0001
Premenopausal							913	0.89	0.70, 1.14	1.13	0.82, 1.58	0.82						
Postmenopausal							1,449	1.17	1.00, 1.39	1.66	1.33, 2.06	<0.0001						
Ovary (C56; 183.0)							442	1.16	0.90, 1.50	1.95	1.44, 2.64	<0.0001						
Prostate (C619; 185)	1,801	1.16	0.94, 1.43	1.27	1.09, 1.47	0.026												
Non-Hodgkin's lymphoma (200; 202)	874	1.25	1.05, 1.48	1.42	1.12, 1.80	0.001	794	0.98	0.81, 1.19	1.54	1.21, 1.95	0.003	1,668	1.15	1.02, 1.31	1.46	1.24, 1.72	<0.0001
Leukemia (C42.1; 204–208)	643	1.32	1.07, 1.60	1.41	1.07, 1.84	0.004	425	1.28	1.00, 1.65	2.01	1.49, 2.71	<0.0001	1,068	1.31	1.12, 1.52	1.61	1.32, 1.96	<0.0001
Multiple myeloma (C42.1; 203)	151	1.64	1.09, 2.47	2.16	1.25, 3.75	0.003	192	1.28	0.88, 1.86	1.92	1.23, 3.00	0.004	343	1.49	1.14, 1.95	2.06	1.46, 2.89	<0.0001
Pancreas (C25; 157)	355	1.03	0.79, 1.33	1.43	1.02, 1.98	0.068	275	0.85	0.62, 1.16	1.63	1.14, 2.34	0.059	630	0.99	0.81, 1.20	1.51	1.19, 1.92	0.005
Bladder (C67; 188)	670	1.18	0.95, 1.46	1.35	1.01, 1.80	0.031	359	1.03	0.77, 1.37	1.15	0.79, 1.69	0.51	1,029	1.12	0.95, 1.33	1.27	1.01, 1.58	0.031
Stomach (C16; 151)	800	1.01	0.83, 1.21	1.36	1.07, 1.74	0.035	376	0.90	0.63, 1.28	0.92	0.73, 1.44	0.61	1,176	0.97	0.83, 1.12	1.25	1.03, 1.51	0.086
Salivary glands (C08; 142)	74	1.45	0.82, 2.57	2.65	1.38, 5.12	0.005	58	0.67	0.35, 1.28	0.68	0.28, 1.67	0.23	132	0.99	0.66, 1.48	1.50	0.92, 2.46	0.18
Testis (C62; 186)	685	1.08	0.87, 1.35	1.16	0.84, 1.61	0.33												
Liver (C22.0; 155)	225	0.99	0.72, 1.38	1.30	0.85, 1.97	0.31	84	0.61	0.35, 1.07	0.94	0.48, 1.84	0.40	309	0.89	0.68, 1.17	1.17	0.83, 1.66	0.65
Lung (C34; 162)	1,736	0.75	0.64, 0.88	0.72	0.57, 0.90	0.0005	1,602	0.71	0.58, 0.85	0.85	0.66, 1.10	0.011	3,338	0.74	0.65, 0.84	0.77	0.66, 0.91	<0.0001
Brain (C71; 191)	617	1.06	0.87, 1.30	1.12	0.84, 1.50	0.39	392	0.98	0.75, 1.28	1.16	0.82, 1.64	0.54	1,009	1.05	0.90, 1.23	1.18	0.95, 1.47	0.15
Bone and cartilage (C40–C41, C49; 170)	89	1.02	0.63, 1.67	1.61	0.86, 3.02	0.21	72	0.56	0.29, 1.07	0.97	0.48, 1.95	0.46	161	0.82	0.56, 1.20	1.24	0.78, 1.97	0.68
Rare/other site	101	1.53	0.80, 2.89	1.59	0.98, 2.58	0.11	102	1.17	0.71, 1.91	1.35	0.73, 2.48	0.31	203	1.39	1.00, 1.95	1.40	0.91, 2.17	0.06

* ICD-O/2, *International Classification of Diseases for Oncology*, Second Edition; ICD-9, *International Classification of Diseases*, Ninth Revision; BMI, body mass index; OR, odds ratio; CI, confidence interval.
† Reference group is the subjects with a body mass index of <25 kg/m^2.
‡ Odds ratios adjusted for 5-year age group, province of residence, education, pack-years of smoking, alcohol drinking, total caloric intake, vegetable intake, dietary fiber intake, and recreational physical activity.
§ Odds ratios also adjusted for menopausal status, number of livebirths, age at menarche, and age at end of first pregnancy.
¶ Odds ratios also adjusted for sex.

TABLE 3. Risk of overall cancer and site-specific cancers associated with body mass index (kg/m^2), by smoking status, National Enhanced Cancer Surveillance System, Canada, 1994–1997

Cancer site	Never smoked* (*n* = 8,105)						Former smoker* (*n* = 10,810)						Current smoker* (*n* = 6,990)					
	No. of cases	BMI†: 25–<30 (adjusted)‡		BMI: ≥30 (adjusted)‡		*p* for trend	No. of cases	BMI: 25–<30 (adjusted)§		BMI: ≥30 (adjusted)§		*p* for trend	No. of cases	BMI: 25–<30 (adjusted)§		BMI: ≥30 (adjusted)§		*p* for trend
		OR†	95% CI†	OR	95% CI			OR	95% CI	OR	95% CI			OR	95% CI	OR	95% CI	
All cancers	6,186	1.14	1.01, 1.28	1.56	1.33, 1.84	<0.0001	8,844	1.17	1.04, 1.31	1.32	1.14, 1.53	<0.0001	5,863	0.98	0.85, 1.13	1.18	0.96, 1.45	0.27
Kidney	454	2.00	1.56, 2.56	3.20	2.39, 4.29	<0.0001	565	1.84	1.45, 2.34	2.72	2.06, 3.59	<0.0001	320	1.44	1.08, 1.92	2.33	1.60, 3.39	<0.0001
Colon	565	1.40	1.10, 1.78	2.00	1.46, 2.74	<0.0001	862	1.47	1.22, 1.86	1.76	1.35, 2.29	<0.0001	293	1.11	0.80, 1.53	1.92	1.26, 2.92	0.006
Rectum	431	1.17	0.90, 1.52	1.71	1.22, 2.40	0.003	729	1.64	1.31, 2.04	1.79	1.35, 2.38	<0.0001	279	1.04	0.75, 1.43	1.09	0.68, 1.76	0.71
Breast (women)¶	1,097	1.17	0.97, 1.43	1.69	1.32, 2.18	<0.0001	756	1.02	0.79, 1.30	1.33	0.98, 1.80	0.11	500	0.96	0.71, 1.29	1.18	0.78, 1.78	0.62
Ovary¶	204	0.95	0.65, 1.39	2.05	1.35, 3.11	0.006	148	1.52	0.98, 2.36	1.85	1.07, 3.18	0.016	87	1.27	0.76, 2.20	1.78	0.86, 3.68	0.11
Prostate	410	1.21	0.75, 1.94	1.52	1.11, 2.07	0.021	1,083	1.15	0.88, 1.49	1.26	1.04, 1.53	0.034	300	0.92	0.66, 1.28	1.02	0.61, 1.68	0.87
Non-Hodgkin's lymphoma	620	1.21	0.98, 1.49	1.66	1.27, 2.18	0.0002	654	1.17	0.95, 1.44	1.19	0.91, 1.54	0.14	387	1.00	0.79, 1.34	1.71	1.23, 2.45	0.015
Leukemia	373	1.23	0.95, 1.59	1.96	1.42, 2.69	<0.0001	464	1.35	1.06, 1.72	1.48	1.09, 1.99	0.006	226	1.24	0.89, 1.71	1.20	0.74, 1.94	0.25
Multiple myeloma	151	1.45	0.97, 2.17	1.60	0.92, 2.79	0.041	152	1.25	0.81, 1.91	2.02	1.24, 3.30	0.007	40	2.08	0.95, 4.59	2.47	0.89, 6.91	0.044
Pancreas	198	1.06	0.76, 1.48	1.34	0.86, 2.09	0.25	237	0.96	0.69, 1.33	1.89	1.30, 2.75	0.003	190	1.01	0.71, 1.45	1.47	0.91, 2.38	0.20
Bladder	176	1.12	0.78, 1.62	1.38	0.85, 2.26	0.20	478	1.29	0.99, 1.66	1.37	1.00, 1.88	0.037	373	1.03	0.77, 1.38	1.34	0.88, 2.04	0.29
Stomach	306	0.75	0.56, 1.00	1.22	0.86, 1.74	0.82	544	1.18	0.94, 1.48	1.32	0.99, 1.76	0.047	314	0.93	0.69, 1.26	1.22	0.79, 1.88	0.62
Salivary	50	0.66	0.34, 1.28	0.74	0.30, 1.84	0.31	51	0.97	0.48, 1.97	2.48	1.18, 5.23	0.028	30	2.07	0.91, 4.72	1.46	0.39, 5.49	0.22
Testis	287	0.89	0.62, 1.27	0.89	0.52, 1.52	0.55	173	1.47	0.94, 2.31	1.90	1.01, 3.58	0.031	224	1.02	0.70, 1.49	1.08	0.60, 1.94	0.80
Liver	92	0.70	0.43, 1.15	0.99	0.51, 1.89	0.53	136	1.12	0.73, 1.72	1.45	0.86, 2.44	0.18	75	0.80	0.52, 1.57	1.16	0.54, 2.51	0.88
Lung	197	0.91	0.65, 1.29	1.19	0.76, 1.87	0.67	1,269	0.86	0.72, 1.03	0.82	0.65, 1.04	0.071	1,843	0.65	0.54, 0.79	0.76	0.57, 1.00	0.0007
Brain	408	1.04	0.81, 1.33	1.30	0.93, 1.84	0.18	337	1.09	0.85, 1.45	1.08	0.72, 1.51	0.66	251	1.01	0.76, 1.43	1.27	0.83, 2.03	0.40
Bone and cartilage	64	0.59	0.31, 1.12	1.04	0.47, 2.28	0.55	58	0.98	0.52, 1.84	1.33	0.64, 2.80	0.51	38	0.83	0.38, 1.81	1.49	0.55, 4.06	0.68
Rare/other site	65	1.30	0.69, 2.46	2.75	1.36, 5.55	0.008	71	1.05	0.60, 1.85	0.89	0.42, 1.88	0.85	65	1.86	1.04, 3.34	0.88	0.34, 2.31	0.47

* Reference group is the subjects with a body mass index of <25 kg/m^2.

† BMI, body mass index; OR, odds ratio; CI, confidence interval.

‡ Odds ratios adjusted for 5-year age group, province of residence, education, alcohol drinking, total caloric intake, vegetable intake, dietary fiber intake, and recreational physical activity. Odds ratios also adjusted for sex for all types of cancers except cancer of the breast (in women), ovary, prostate, and testis.

§ Odds ratios also adjusted for pack-years of smoking.

¶ Odds ratios also adjusted for menopausal status, number of livebirths, age at menarche, and age at end of first pregnancy.

TABLE 4. Population attributable risk of overall cancer and site-specific cancers related to overweight and obesity, by sex and cancer site, National Enhanced Cancer Surveillance System, Canada, 1994–1997

Cancer site	Men				Women				All			
	Overweight (prevalence = 40%)		Obesity (prevalence = 16%)		Overweight (prevalence = 25%)		Obesity (prevalence = 14%)		Overweight (prevalence = 33%)		Obesity (prevalence = 15%)	
	PAR* (%)	95% CI*	PAR (%)	95% CI	PAR (%)	95% CI	PAR (%)	95% CI	PAR (%)	95% CI	PAR (%)	95% CI
All cancers	5.30	1.46, 9.16	4.43	1.97, 6.89	0.50	–2.04, 3.04	5.43	3.11, 7.75	2.88	0.60, 5.16	4.85	3.18, 6.53
Kidney	29.18	20.96, 37.40	25.59	18.86, 32.32	10.91	4.86, 16.95	16.58	11.09, 22.07	20.26	15.07, 25.45	20.70	16.41, 24.98
Colon	17.76	10.64, 24.89	15.65	10.34, 20.97	5.21	0.14, 10.28	9.73	5.25, 14.21	11.66	7.27, 16.08	12.24	8.81, 15.67
Rectum	14.09	6.82, 21.36	10.71	5.62, 15.81	6.54	0.85, 12.23	6.54	1.93, 11.15	10.62	5.96, 15.27	8.88	5.43, 12.33
Postmenopausal breast					4.08	–0.28, 8.44	8.46	4.52, 12.40				
Ovary					3.85	–2.44, 10.13	11.74	5.96, 17.52				
Prostate	6.02	0.58, 11.45	4.14	0.63, 7.65								
Non-Hodgkin's lymphoma	9.09	2.04, 16.15	6.30	1.76, 10.84	–0.50	–5.10, 4.10	7.03	2.93, 11.13	4.72	0.49, 8.94	6.45	3.43, 9.47
Leukemia	11.35	3.34, 19.36	6.16	1.04, 11.27	6.54	–0.07, 13.15	12.39	6.41, 18.37	9.28	4.07, 14.49	8.38	4.57, 12.19
Multiple myeloma	20.38	4.85, 35.91	15.65	3.78, 27.52	6.54	–2.89, 15.96	11.41	3.31, 19.51	13.92	4.97, 22.87	13.72	6.83, 20.61
Pancreas	1.19	–8.82, 11.20	6.44	0.09, 12.78	–3.90	–10.64, 2.85	8.11	1.79, 14.43	–0.33	–6.45, 5.79	7.11	2.66, 11.55

* PAR, population attributable risk; CI, confidence interval.

Our study adds further evidence to the previously established associations between obesity and cancers of the kidney, breast (postmenopausal), colon, and rectum (4, 11, 13, 21, 22, 24). Some studies reported a stronger association of obesity with kidney cancer in women than in men; however, we found that the risk of kidney cancer associated with obesity was similar for men and women. Some investigators observed a negative association between obesity and premenopausal breast cancer, whereas we found no association. Most studies reported that the association between obesity and colorectal cancer was stronger in men than in women, which is similar to our result. Our study also confirmed the positive association between obesity and pancreatic cancer that has been reported in the literature (21, 22, 25–32).

Previous studies on the link between obesity and prostate cancer have yielded inconsistent results (21, 24, 33–35). Although our study showed a small association between obesity and prostate cancer, the increased risk appeared only among those who never drank alcohol, which might explain in part the previous inconsistent results, because the findings of different studies may have varied according to the different percentages of subjects who did and did not drink alcohol.

The increased risk of ovarian cancer related to obesity in our study concurs with the risks from two cohort studies (36, 37) and a meta-analysis (38) that reviewed 13 hospital case-control studies, 11 population case-control studies, and five cohort studies. However, a recent cohort study found an inverse association between body mass index and ovarian cancer risk (39).

We observed an increased risk of non-Hodgkin's lymphoma, leukemia, and multiple myeloma associated with obesity in both sexes, and smoking and drinking alcohol did not substantially modify this association. There are few published studies on obesity and these three cancers. The positive association with obesity was also found in one previous study for non-Hodgkin's lymphoma (the association was confined to women) (21), in one study for multiple myeloma (40), and in another study for leukemia (22).

Our study found obesity to be associated with bladder cancer, which is consistent with two previous cohort studies (21, 22), but it could be by chance. However, the positive association for stomach cancer among men observed in our study is in contrast to the inverse association seen in a previous prospective study (41) and the lack of an association found in other studies (21, 22). When we stratified the analyses by smoking and alcohol drinking, however, the associations with obesity for cancers of the stomach and salivary glands became weaker among never smokers and current smokers and disappeared in the group who never drank alcohol. Therefore, the positive association we saw between obesity and cancers of the stomach and salivary glands could be the residual effect of smoking cigarettes and drinking alcohol or could be attributed to chance.

The inverse association we found between obesity and lung cancer is probably the confounding effect of cigarette smoking, because it disappeared for never smokers when stratified by smoking status. This finding is similar to the results of one previous study (42).

For all cancers combined, we found a positive association with not only obesity but also overweight, for both men and women. The association between all cancers combined and obesity is comparable with the results of two cohort studies (21, 22). Furthermore, prospective studies showed that adults (43) and adolescents (44) with a higher body mass index had an increased risk of mortality from cancer.

Several hypotheses have been proposed for the association between obesity and cancer, including changes in endogenous hormone metabolism, elevation in the endogenous

production of reactive oxygen species and oxidative DNA damage, alteration in carcinogen-metabolizing enzymes, and tissue-size homeostasis (13). However, except for the hormone metabolism theory, no human studies support these hypotheses.

The metabolic abnormalities related to excess weight include high plasma triglyceride, glucose, and insulin levels, as well as insulin resistance (45). The chronic hyperinsulinemic state in obesity reduces the insulin-like growth factor (IGF)-binding protein and increases free IGF-I (46). The World Cancer Research Fund (46) suggested that this physiologic milieu promotes cell growth in general and, particularly, growth of tumor cells. There is evidence that both insulin and IGF-I can stimulate cell proliferation and inhibit apoptosis, thus enhancing tumor development (45, 47–49). These effects have been demonstrated for cancers of the breast, ovary, colon-rectum, stomach, pancreas, and prostate (45, 47, 50).

Obesity may also affect risks of cancers of the breast, ovary, and prostate by altering the levels of sex hormones (13, 51, 52). Hyperinsulinemia may reduce the sex hormone-binding globulin and consequently increase the level of free estrogens and androgens (47, 51). In addition, adipose tissue is a major location for the synthesis of estrogens (estrone and estradiol) from androgenic precursors in men and postmenopausal women (52, 53). Sex hormones can regulate the balance between cellular differentiation, proliferation, and apoptosis, and they may also selectively help the growth of preneoplastic and neoplastic cells (13, 54). The role of estrogen in the etiology of ovarian cancer is supported by the increased risk with long-term use of postmenopausal estrogen shown in two cohort studies (36, 55) and the reduced risk of ovarian cancer with breastfeeding, parity, and oral contraceptive use (56). Experimental studies on rats demonstrated that giving testosterone could produce adenocarcinoma in the prostate glands (57). Human studies also suggested that higher circulating levels of free androgens might increase the risk of developing prostate cancer (58).

Moyad (59) proposed several potential mechanisms for the association between kidney cancer and obesity, including higher levels of estrogen, a greater concentration of growth factors in adipose tissue, elevated insulin levels and insulin insensitivity, greater sympathetic activity or hypertension, increased cholesterol levels and down-regulation of low-density lipoprotein receptors, immune system dysfunction and dysregulation, lower levels of vitamin D, diets that are higher in calories and lower in antioxidants, physical inactivity, and extrinsic toxins and carcinogen accumulation in adipose tissue.

For non-Hodgkin's lymphoma, leukemia, and multiple myeloma, the mechanism for their link with obesity is unclear. It could be related to the decreased immune response associated with obesity (60, 61) and lower intake of antioxidants and other nutrients (62).

The limitations of our study should not be overlooked. Misclassification of exposure was possible because respondents self-administered the questionnaires, and obese people may have underreported their weight. However, the underreporting of weight is likely to be nondifferential, which tends to attenuate the observed effects. The interval between the reference date and diagnosis date in our study was only 2 years. As a result, some preexisting diseases that may cause weight loss could affect the association between obesity and cancers. The death of 10.8 percent of eligible cancer cases before they could be sent questionnaires to be included in the present study might affect the generalization of our result; that is, our result may be generalizable to either less aggressive cancer tumors or to healthier subjects able to be diagnosed earlier or to respond better to treatment. In addition, with so many comparisons made, some of the results could be found by chance.

In summary, our large population-based study showed an increased risk of overall cancer among obese men and women, and it provides further support for the positive associations of obesity with cancers of the kidney, colon, rectum, breast (in postmenopausal women), ovary, pancreas, and prostate. We also noticed excess risks of non-Hodgkin's lymphoma, leukemia, and multiple myeloma among obese people, which need to be confirmed by further investigation. Because obesity is a growing global problem and is also a modifiable lifestyle factor, the prevention or reduction of obesity by increasing physical activity and decreasing caloric intake would have enormous public health impact.

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