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OVERWEIGHT AS AN AVOIDABLE CAUSE OF CANCER IN EUROPE

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There is growing evidence that excess body weight increases the risk of cancer at several sites, including kidney, endometrium, colon, prostate, gallbladder and breast in post-menopausal women. The proportion of all cancers attributable to overweight has, however, never been systematically estimated. We reviewed the epidemiological literature and quantitatively summarised, by meta-analysis, the relationship between excess weight and the risk of developing cancer at the 6 sites listed above. Estimates were then combined with sex-specific estimates of the prevalence of overweight [body mass index (BMI) 25–29 kg/m^2] and obesity (BMI ≥30 kg/m^2) in each country in the European Union to obtain the proportion of cancers attributable to excess weight. Overall, excess body mass accounts for 5% of all cancers in the European Union, 3% in men and 6% in women, corresponding to 27,000 male and 45,000 female cancer cases yearly. The attributable proportion varied, in men, between 2.1% for Greece and 4.9% for Germany and, in women, between 3.9% for Denmark and 8.8% for Spain. The highest attributable proportions were obtained for cancers of the endometrium (39%), kidney (25% in both sexes) and gallbladder (25% in men and 24% in women). The largest number of attributable cases was for colon cancer (21,500 annual cases), followed by endometrium (14,000 cases) and breast (12,800 cases). Some 36,000 cases could be avoided by halving the prevalence of overweight and obese people in Europe.

Key Words: *breast cancer; colorectal cancer; endometrial cancer; prostate cancer; kidney cancer; gallbladder cancer; body mass index; risk factors*

Since a large prospective study[1] showed the first evidence that overweight and obesity increase the risk of mortality from certain cancers, numerous other studies linking excess weight to cancer at several sites have been reported. The evidence for an association is now strong for cancers of the endometrium,[2] kidney[3] and the post-menopausal breast,[4] as well as colon,[5] gallbladder[6] and prostate.[7] Cancers of the thyroid[8,9] and gastric cardia[10–12] as well as adenocarcinoma of the esophagus[13] have been associated with overweight and obesity.

Notwithstanding the growing evidence that overweight is causally related to cancer of several sites, there has been no systematic attempt to estimate the total proportion of all cancers attributable to this potentially avoidable but increasingly more common cause. We have reviewed the epidemiological literature and quantitatively summarised the relationship between excess weight and the risk of developing cancer. We performed a meta-analysis for the 6 cancer sites for which the evidence is most consistent and estimated the proportion of cancer cases attributable to overweight or obesity that occurred in the countries of the European Union.

MATERIAL AND METHODS

Search methods

We identified studies published between 1966 and 1997 (we began data abstraction in 1998) through the MEDLINE (National Library of Medicine, Washington, D.C.) database. Since heterogeneity of study design, methods of exposure assessment and data analysis are common causes of inconsistency between observational studies, we chose, *a priori*, desirable properties for design, study size and period of publication and, whenever possible, included only studies with these characteristics. Throughout, we refer to studies having these characteristics as "eligible".

Besides a MEDLINE search, we also systematically examined the list of references in the identified articles. The literature review and meta-analysis were confined to cancers of the breast, colon, endometrium, prostate, kidney and gallbladder. We included prospective studies with at least 100 observed cases and population-based case-control studies with at least 200 cases. These restrictions were feasible for cancers of the breast, colon, prostate and endometrium. However, most studies of kidney cancer were relatively small, particularly those on women; therefore, we included cohort studies with at least 50 and case-control studies with at least 100 female cases. Due to the limited number of epidemiological studies on gallbladder cancer, we included all published data. When several articles were published from the same study, we used the most recent report or the one providing the most detailed information.

Design of meta-analysis

For each of the cancer sites considered, we performed a co-variance analysis of the log relative risk on body mass, with terms for study (categories), body mass index (BMI, continuous) and their interaction. We checked the assumption of linearity of the relationship by testing the statistical significance of adding a squared term of BMI. In only one case was this close to statistical significance (colon cancer), and this case is discussed in the relevant section of Results.

Once we had accepted the log-linear dose-response, we estimated a relationship for each of the selected studies according to the co-variance–adjusted approach.[14] Individual slopes were then combined by weighted average, using the inverse of their variances as weights.[15] Fixed- (FE) and random- (RE) effects 95% confidence intervals (CIs) were calculated for the slope of the common regression slope. The dose-response curve thus obtained provided estimates of the relative risk (RR) associated with standard definitions of normal (reference category), overweight and obese people. These were then combined with country-specific estimates of the population prevalence to obtain the proportion of site-specific cases attributable to excess weight, according to Cole and MacMahon's[16] classical formula. In addition to RR and its variance, estimation of the pooled slope required the distribution of cases and controls/person-years in the exposure categories.

Data abstraction and coding

As a measure of excess weight, we used BMI, calculated as weight divided by height squared (kg/m^2). This index, recom-

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mended in population studies,[17–19] estimates the level of fatness independent of height in a general adult population. For each of the associations considered, we listed the major potential confounders. We then abstracted and coded the following information: study design, country, measure of fatness adopted, intervals of body mass and corresponding adjusted RRs (rate ratios, odd ratios, standardised morbidity/mortality ratios, hereinafter denoted as RR), their 95% CIs, number of cases, number of controls/person-years and confounders considered. The variance of the ln RRs was derived from the 95% CIs by the following formula:

$$\text{study variance} = [\ln(\text{upper 95\% CI}) - \ln(\text{lower 95\% CI})]^2/(3.92)^2$$

Since body mass is measured on a continuous scale, exposure intervals vary from study to study depending on the actual range observed. We summarised closed intervals with their mid-point and open intervals with +10% of their cut-point.[15,20] We used in the quantitative analyses all study results expressing weight as BMI and including all of the following items: extremes of the exposure intervals adopted, corresponding RRs and their variances or 95% CIs. Of these, only those also providing the distribution of cases and controls/person-years in the exposure categories could be used to obtain the co-variance–adjusted estimates of the slopes.

For each cancer site, 3 meta-analyses were performed. The first analysis (model A) included all eligible studies suitable for meta-analysis, the second (model B) was restricted to studies with incident cases as outcome and the third (model C) was further restricted to studies accounting for major confounders. In most cases, use of model C entailed a major loss of information. Model B was therefore chosen to predict the RRs used in calculating the attributable risk when the results from model C were similar.

Attributable fractions of cancer were estimated for overweight ($25 < \text{BMI} < 30$ kg/m,^{2} BMI = 27) and obese (BMI ≥ 30 kg/m,^{2} BMI = 32) persons compared to those of normal weight (BMI 20–25 kg/m,^{2} BMI = 22) according to the WHO guidelines for a healthy physical status.[21,22] These were applied to the number of incident cases, by country and sex, estimated for 1995 by the International Agency for Research on Cancer.[23] The incidence of gallbladder cancer, not available from this source, was obtained from *Cancer Incidence in Five Continents*[24] as national figures for Sweden, Norway, Finland, Denmark and the Netherlands or as age- and sex-specific mean rates in the case of country registries. Rates for Portugal and Greece, where no cancer registry is active, were obtained by applying the average European mortality/incidence ratios of gallbladder cancer based on *Cancer Incidence in Five Continents* to national mortality from the WHO mortality data bank.[25]

Prevalence of obesity in Europe

Since data on the prevalence of overweight and obesity among men and women at the country level could not always be identified, the most informative estimates were obtained from the WHO MONICA[26] and CINDI[27] studies. These sources also have the advantage of complying with a common protocol of data collection, thus improving the comparability of the data for the different countries. In the MONICA project, cross-sectional data were collected between 1983 and 1986. Trained personnel measured height and weight in research centres. Each centre studied between 1,046 and 3,563 men and women, aged between 35 and 64 years. The MONICA data are population-based but not necessarily representative of the whole country. Data were available by sex but not in subgroups of the study age group (34–64 years). The CINDI programme collected data between 1982 and 1987 on behavioural, anthropometric and socio-economic characteristics of 24 countries including Austria, Northern Ireland and Portugal, with the aim of improving community health. Height and weight were measured in 1,287 to 2,361 men and women aged 25 to 64 years. Neither of the 2 projects included centres in the Netherlands, for which we used data obtained from a random sample of 5,000 men and women aged 20–59 years, collected each year from 1993 to 1996 (data not shown). For Greece, the only published data[28,29] were highly selected by age, an important determinant of excess weight,[30] or social class. We therefore adopted the mean of the values in the other southern European countries, *i.e.*, Portugal, Spain and Italy.

RESULTS

Prevalence of overweight and obesity

Estimates of the prevalence of overweight and obese subpopulations by sex and country are shown in Table I. In both men and women, excess weight (BMI >25 kg/m^2) was slightly more common in southern Europe than in northern countries. The mean prevalence was 61% for men and 52% for women in southern Europe compared with 59% for men and 47% for women in the north. Greater geographic variation was observed in women (35% to 68%) than in men (55% to 70%). The prevalence of obesity (BMI $\geq$30 kg/m^2) varied between 9% (Spain) and 18% (Finland) in men, while that among women varied between 10% (Denmark) and 24% (Spain). With few exceptions (Denmark and the Netherlands), obesity was more prevalent in women, while overweight was more prevalent in men.

Breast cancer

Pre-menopausal women. Seventeen studies on pre-menopausal breast cancer were eligible for our review.[31–47]

Only 9 studies could be used in the meta-analysis. They are summarised in Table IIA. The summary analysis showed that obesity was inversely associated with pre-menopausal breast cancer, with a RR of 0.98 per unit of increase in BMI (95% CI 0.97–0.99) (Table IIA). Limiting the analysis to studies with only incident cases, which meant omitting only 1 study,[39] did not change the point estimate. A further restriction to studies adjusted for age, reproductive factors and alcohol or diet[42,45,46] only changed the confidence limits.

Because excess weight entails other major adverse effects on health,[48] no attributable fractions for pre-menopausal breast cancer were estimated.

Menopausal women. Twenty-seven studies were eligible,[31–40,42,44,46,47,49–61] conducted in North America (n = 14), Europe (n = 9), China (n = 2) and Israel (n = 1), with 1 multi-national study. Four studies included a small number of pre-menopausal cases, representing a maximum of 21% of cases.[52,53,57,58]

A statistically significant positive association between obesity and breast cancer in post-menopausal women was reported in 7 of

TABLE I – PREVALENCE OF OVERWEIGHT (BMI 25.1–30 KG/M^2) AND OBESE (BMI $\geq$ 30 KG/M^2) MEN AND WOMEN IN THE EUROPEAN UNION, BY COUNTRY

Country	Men		Women	
	Overweight	Obese	Overweight	Obese
Austria[1]	48	12	29	17
Belgium[2]	49	15	36	20
Denmark[2]	44	11	25	10
Finland[2]	50	18	38	20
France[2]	49	12	30	17
Germany[2]	53	17	35	20
Greece[3]	50	13	40	22
Ireland[1]	47	11	32	17
Italy[2]	48	15	36	21
Luxembourg[2]	45	14	33	18
The Netherlands[4]	45	11	31	11
Portugal[1]	45	14	39	21
Spain, Catalonia[2]	57	9	44	24
Sweden[2]	45	10	29	12
United Kingdom[2]	46	11	36	15
European Union	50	13	35	19

[1]WHO CINDI study.[27] Men and women 20–59 years old in 1982–1987.–[2]WHO MONICA study.[26] Men and women 35–64 years old in 1983–1986.–[3]Mean of Italy, Portugal and Spain.–[4]Seidell, personal communication (1998). Men and women 20–59 years 1993–1996.

TABLE IIA – SUMMARY OF SELECTED STUDIES OF OBESITY AND PREMENOPAUSAL BREAST CANCER AND RESULTS OF DOSE-RESPONSE META-ANALYSES

Reference	Study[1]	Cases		Country	Confounders[3]	Estimated dose-response per unit increase in BMI	
		Type[2]	Number			Coefficient	95% CI
36	CCP	I	306	Canada	A	0.98	0.94–1.02
37	CCP	I	634	Denmark	A	1.01	0.98–1.04
39	CCP	I, P	751	USA	A, RF	1.00	0.97–1.03
41	CCP	I	420	Sweden, Norway	A, RF	1.01	0.96–1.06
42	CCP	I	270	Canada	A, ADP, RF	0.98	0.94–1.02
32	Coh	I	137	Norway	A	0.91	0.87–0.96
45	CCP	I	1,588	USA	A, ADP, RF	0.97	0.95–0.99
46	CCP	I	1,427	USA	ADP, RF	0.98	0.97–1.00
34	Coh	I	1,000	USA	A, RF	0.98	0.97–1.00
Summary analysis (number of studies)							
A (9)						0.98	0.97–0.99
B (8)						0.98	0.97–0.99
C (3)						0.98	0.96–0.99

[1]CCH, case-control hospital-based; CCP, case-control population-based; Coh, cohort.–[2]D, dead cases; I, incident cases.–[3]A, age; RF, reproductive factors; ADP, alcohol, diet, physical exercise.

TABLE IIB – SUMMARY OF SELECTED STUDIES OF OBESITY AND POST-MENOPAUSAL BREAST CANCER AND RESULTS OF DOSE-RESPONSE META-ANALYSES

Reference	Study[1]	Cases		Country	Confounders[3]	Estimated dose-response per unit increase in BMI	
		Type[2]	Number			Coefficient	95% CI
36	CCP	I	517	Canada	A	1.00	0.98–1.01
37	CCP	I	489	Denmark	A	1.01	0.97–1.04
52	Coh	I	215 >50: 30 ≤ 50:185	USA	A	1.06	1.01–1.11
39	CCP	I, P	1,017	USA	A, RF	1.03	1.01–1.06
54	Coh	I	221	Iowa, USA	A	1.01	0.97–1.04
42	CCP	I	329	Canada	A, ADP, RF	1.03	1.00–1.06
32	Coh	I	99	Norway	A	0.97	0.92–1.03
55	CCP	I	439	USA	A, RF	1.05	1.02–1.08
57	CCP	I, P	306	Sweden	None	1.02	0.98–1.05
60	CC in Coh	I	626	Netherlands	A, ADP, RF	1.00	0.98–1.03
46	CCP	I	4,921	USA	ADP, RF	1.03	1.02–1.04
34	Coh	I	1,517	USA	A, RF	1.01	1.00–1.02
61	CCP	I	2,704	Sweden	A, RF	1.04	1.03–1.06
Summary analysis (number of studies)							
A (13)						1.02	1.02–1.03
B (12)						1.02	1.02–1.03
C (3)						1.03	1.02–1.04

[1]CCH, case-control hospital-based; CCP, case-control population-based; Coh, cohort.–[2]D, dead cases; I, incident cases.–[3]A, age; RF, reproductive factors; ADP, age, diet, physical exercise.

the 13 cohort studies,[31,33,35,42,52,56,59] while no significant association was detected in the remaining 6.[32,34,53,54,58,60] Among the population-based case-control studies, 7 showed a positive association with obesity[39,40,47,49–51,55,61] and 4 showed no association.[37,38,46,57] We considered age, age at menarche, parity and other reproductive factors to be the major potential confounders. Twelve studies accounted for the main reproductive factors[34,35,39,40,42,46,47,49,55,59–61] and 3 for alcohol, diet and physical exercise.[42,46,60]

Thirteen studies contributed to the meta-analysis (Table IIB). We estimated a 2% increase in risk per unit increase in BMI (FE 95% CI 1.02–1.03, RE 95% CI 0.69–1.52) (Table IIB). Limiting the analysis to studies with only incident cases, which meant excluding 1 study,[39] did not affect the estimates. Further limitations to studies adjusted for age, reproductive factors and alcohol or diet[42,46,60] marginally affected the point estimate and reduced heterogeneity between studies (RR 1.03 per unit of increase in BMI; FE 95% CI 1.02–1.04, RE 95% CI 0.75–1.27).

The estimates predict that the excess risk is 12% for overweight and 25% for obese women (Table III). Table IV shows the proportion of cases attributable to excess weight in Europe. In total, 8.5% of breast-cancer cases in women aged 50 years and over and 6.6% for all ages could be attributed to overweight and obesity. Table V shows the numbers of new cases attributable to excess weight. In all, 13,000 cases of breast cancer could be avoided each year in the European Union if overweight and obesity were eliminated.

Colon cancer

Nineteen studies on excess weight and colon cancer were eligible.[1,58,62–78] Of the 12 prospective studies, 4 analysed cancers of the colon and rectum as 1 entity.[1,63,69,76]

Most cohort studies indicated a positive association between overweight and colon cancer;[1,58,63,66,70,71,75,76,77] this was somewhat less consistent among women and was confined to older men in a Japanese cohort.[62] One prospective study showed no association in either sex.[64] A positive relationship was supported by most population-based case-control studies,[65,67,68,74,76,78] generally with a higher RR but often with borderline significance. One case-control study showed no association.[69] We considered age, sex, family history of colon cancer, ethnicity, social class, physical

TABLE IIC – SUMMARY OF SELECTED STUDIES OF OBESITY AND COLON CANCER AND RESULTS OF DOSE-RESPONSE META-ANALYSES

Reference	Study[1]	Cases		Country	Age (years)	Sex	Confounders[3]	Estimated dose-response per unit increase in BMI	
		Type[2]	Number					Coefficient	95% CI
68	CCP	I	163	Sweden	40–80	M	A, sex	1.08	1.03–1.12
			189			F			
69	CCP	I	388	Australia	All cases	M	A, ADP	1.03	0.98–1.08
			327			F		0.98	0.95–1.02
71	Coh	I, D	302	USA	—	M	A, RF	1.05	1.01–1.09
73	Coh	D	611	USA	≥30	M	ADP	1.02	1.00–1.05
			539			F		1.01	0.99–1.04
75	Coh	I	203	USA	40–75	M	—	1.04	1.00–1.08
77	Coh	I	393	USA	30–55	F	AP, FH, TA, HRT, AD	1.03	1.00–1.05
Summary analysis (number of studies)									
A (8)								1.03	1.02–1.04
B (5)								1.03	1.01–1.05
C idem								idem	idem

[1]CCH, case-control hospital-based; CCP, case-control population-based; Coh, Cohort.–[2]D, dead cases; I, incident cases.–[3]A, age; ADP, alcohol, diet, physical exercise; RF, reproductive factors; TA, tobacco, alcohol; FH, family history of disease; HRT, hormone replacement therapy; AD, analgesic drug use.

TABLE IID – SUMMARY OF SELECTED STUDIES OF OBESITY AND PROSTATE CANCER AND RESULTS OF DOSE-RESPONSE META-ANALYSES

Reference	Study[1]	Cases		Country	Age (years)	Confounders[3]	Estimated dose-response per unit increase in BMI	
		Type[2]	Number				Coefficient	95% CI
83	Coh	I	174	Japanese men, Hawaii, USA	46–68	A	1.04	0.99–1.09
84	Coh	I	180	USA	≥25	A	1.02	0.97–1.07
88	CCP	I	207	Canada	—	A	1.02	0.96–1.08
90	Coh	I	2,368	Sweden	—	A	1.01	1.00–1.03
91	Coh	I	1,338	USA	40–75	A, BMI 21	1.00	0.98–1.02
92	CCP	I	325	UK	<75	A	1.04	0.99–1.10
Summary analysis (number of studies)								
A (6)							1.01	1.00–1.02
B idem							idem	idem
C idem							idem	idem

[1]CCH, case-control hospital-based; CCP, case-control population-based; Coh, Cohort.–[2]D, dead cases; I, incident cases.–[3]A, age; BMI21, BMI at age 21.

TABLE IIE – SUMMARY OF SELECTED STUDIES OF OBESITY AND ENDOMETRIAL CANCER AND RESULTS OF DOSE-RESPONSE META-ANALYSES

Reference	Study[1]	Cases		Country	Age (years)	Confounders[3]	Estimated dose-response per unit increase in BMI	
		Type[2]	Number				Coefficient	95% CI
97	CCP	I	400	USA	20–74	A, OC, RF	1.10	1.07–1.14
99	CCP	I	268	China	18–74	A, RF	1.09	1.03–1.16
100	CCP	I	376	USA	20–74	A, RF	1.06	1.02–1.10
101	CCP	I	232	USA	40–85	A, RF	1.14	1.08–1.20
Summary analysis (number of studies)								
A (4)							1.10	1.07–1.12
B (4)							idem	idem
C (1)							1.10	1.07–1.14

[1]CCH, case-control hospital-based; CCP, case-control population-based; Coh, Cohort.–[2]D, dead cases; I, incident cases.–[3]A, age; RF, reproductive factors; OC, oral contraceptive use.

exercise and diet as potential confounders. Most studies accounted for age and 1 other of these confounders.[63,67–69,71–78]

Only 6 of the studies reviewed could be included in the meta-analyses[68,69,71,73,75,77] (Table IIC). When results were available by sex, these were abstracted separately and considered as independent observations in our meta-analysis.[69,73] Since the meta-analyses showed no significant heterogeneity by sex, only the combined results are reported. We found a positive association between excess weight and colon cancer, the average RR being 1.03 (95% CI 1.02–1.04) per unit increase in BMI. Restriction of the analysis to studies having incident cases as outcome[68,69,75,77] did not affect the estimate (FE 95% CI 1.01–1.05, RE 95% CI 1.00–1.06). All of these studies accounted for age and at least 1 additional factor (alcohol, diet or physical exercise) so that model C coincided with model B.

The dose-response relationship estimated by model B corresponded to a 15% increase in the risk of developing colon cancer for an overweight person compared with a person having a normal weight and a 33% increase in risk for an obese person (Table III). The proportion of colon cancers attributable to excess weight among Europeans is 11% in either sex (Table IV). Excess weight accounts for about 11,000 new cases of colon cancer in men and 10,000 in women every year (Table V).

TABLE IIF – SUMMARY OF SELECTED STUDIES OF OBESITY AND KIDNEY CANCER AND RESULTS OF DOSE-RESPONSE META-ANALYSES

Reference	Study[1]	Cases		Country	Age (years)	Sex	Confounders[3]	Estimated dose-response per unit increase in BMI	
		Type[2]	Number					Coefficient	95% CI
104	CCP	P	313	USA	30–64	M	A, KS, T	1.03	0.99–1.07
			182			F		1.10	1.03–1.16
105	CCP	I	209	USA	≥40	M	A	1.10	1.05–1.16
			105			F		1.03	0.96–1.09
107	CCP	I	310	Australia	20–79	M	A	1.07	1.01–1.13
			179			F		1.03	0.98–1.08
109	CCP	I	M:282	Canada	25–69	M	A, T	1.03	0.98–1.09
			F:181			F		1.12	1.05–1.20
110	CCP	I	M:1,050	Multinational	20–79	M	A, T	1.06	1.03–1.09
			F:682			F		1.07	1.04–1.09
111	Coh	D	M:212	USA	≥30	F+M	A	1.06	1.02–1.10
			F:123					1.09	1.04–1.13
112	Coh	I	F:62	USA	55–69	F	A	1.12	1.03–1.21
Summary analysis (number of studies)									
A (13)								1.06	1.05–1.34
B (7)								1.06	1.05–1.08
C (4)								1.06	1.05–1.08

[1]CCH, case-control hospital-based; CCP, case-control population-based; Coh, cohort.–[2]D, dead cases; I, incident cases.–[3]A, age; KS, kidney stones; T, tobacco; TC, tobacco, coffee.

TABLE IIG – SUMMARY OF STUDIES OF OBESITY AND GALLBLADDER CANCER AND RESULTS OF DOSE-RESPONSE META-ANALYSIS

Reference	Study[1]	Cases		Country	Age (years)	Sex	Confounders[3]	Estimated dose-response per unit increase in BMI	
		Type[2]	Number					Coefficient	95% CI
115	CCH	I	M, 13	Bolivia, Mexico	All cases	M, 15%; F, 85%	A, sex	1.09	0.90–1.33
			F, 71						
116	CCP	I	M, 44	Australia, Canada, Netherlands, Poland	All cases	M	A, Sex, TA, SES	0.99	0.87–1.11
			F, 145			F		1.08	1.01–1.15
Summary analysis: 2 studies, 3 observations								1.06	1.00–1.12
Model									
A = B									

[1]CCH, case-control hospital-based; CCP, case-control population-based; Coh, cohort.–[2]D, dead cases; I, incident cases.–[3]A, age; TA, tobacco, alcohol; SES, socio-economic status.

TABLE III – RR ASSOCIATED WITH OVERWEIGHT AND OBESITY PREDICTED BY COMMON DOSE-RESPONSE SLOPES, BY CANCER SITE

Cancer site	RR for overweight[1] *vs.* normal weight	RR for obese[2] *vs.* normal weight
Breast in post-menopausal women	1.12	1.25
Colon	1.15	1.33
Endometrium	1.59	2.52
Prostate	1.06	1.12
Kidney	1.36	1.84
Gallbladder	1.34	1.78

[1]Obese, BMI ≥ 30.–[2]Overweight, 25 ≤ BMI < 30.

The statistical test on the log-linear assumption of the dose-response was not significant in model A ($p = 0.67$ based on 11 observations) but close to the conventional 5% cut-point for models B ($p = 0.07$, n = 8) and C ($p = 0.11$, n = 6). The second-degree model under restriction B would predict RRs of 1.30 and 1.54 for overweight and obese, respectively, corresponding to twice the excess risk of the log-linear model. If we accepted this model, attributable fractions and number of attributable cases for colon cancer would be approximately twice those reported.

Prostate cancer

Seventeen studies of obesity and prostate cancer were eligible for review;[1,58,79–92] all were conducted in North America or Europe. Two[1,58] of the 9 cohort studies reported a significant association between excess weight and prostate cancer, while the others found no association.[79,80,83,84,87,90,91] A positive association was supported by 2 of the population-based case-control studies,[85,89] but the majority showed no relationship with obesity.[80,81,82,86,88,92] We considered age, family history of prostate cancer, ethnicity, social class, diet, physical activity and occupational exposures to be the most important potential confounders for the association between obesity and prostate cancer. Most of the cohort[82,84,90] and case-control[81,82,88,92] studies accounted only for age.

Only 6 of the studies qualified for meta-analysis, 4 cohort studies, all with incident cases,[83,84,90,91] and 2 population-based case-control studies[88,92] (Table IID). All studies accounted for age but none of the other potential confounders. Models A, B and C were therefore identical. Elevated BMI was positively associated with prostate cancer but with borderline statistical significance. The RR was 1.01 per unit of increase in BMI (FE 95% CI 1.00–1.02, RE 95% CI 0.80–1.28) (Table IID).

The estimated RR corresponded to a 6% increase in risk of prostate cancer for an overweight man compared with a normal weight and to a 12% increase in risk for an obese man (Table III).

TABLE IV – PROPORTION OF CANCER CASES ATTRIBUTABLE TO OVERWEIGHT AND OBESITY IN THE COUNTRIES OF THE EUROPEAN UNION, BY CANCER SITE

Country	Breast women	Colon		Endometrium women	Prostate men	Kidney		Gallbladder		Total	
		Men	Women			Men	Women	Men	Women	Men	Women
Austria	7.4	10.5	9.5	35.1	4.2	23.9	21.9	22.6	20.7	3.7	6.0
Belgium	8.8	11.6	11.2	40.8	4.6	25.9	25.9	24.8	24.4	2.9	6.7
Denmark	5.4	9.7	6.8	26.0	3.9	22.1	16.0	20.9	15.1	2.9	3.9
Finland	9.1	12.6	11.6	41.6	5.0	28.4	26.4	26.8	24.9	4.4	7.2
France	7.6	10.7	9.6	35.6	4.3	24.2	22.2	22.8	21.0	3.1	6.1
Germany	8.8	12.7	11.2	40.4	5.1	28.5	25.6	27.0	24.1	4.9	6.8
Greece	10.0	11.1	12.4	44.2	4.4	25.1	28.2	23.7	26.6	2.1	5.9
Ireland	7.8	10.1	9.9	36.4	4.0	22.9	22.8	21.7	21.5	3.1	5.0
Italy	9.1	11.4	11.6	41.7	4.6	25.9	26.5	24.5	25.0	3.1	7.5
Luxembourg	8.1	10.7	10.3	37.8	4.3	24.5	23.8	23.1	22.4	2.6	6.7
Netherlands	6.3	9.8	7.9	29.8	3.9	22.4	18.5	21.2	17.4	3.1	4.8
Portugal	9.5	10.7	12.0	42.9	4.3	24.5	27.3	23.1	25.8	2.9	7.1
Spain	10.7	10.8	13.5	47.3	4.4	24.1	30.5	22.8	28.8	2.6	8.8
Sweden	6.3	9.5	8.0	30.0	3.8	21.7	18.6	20.5	17.5	3.8	5.2
United Kingdom	7.8	10.0	9.8	36.1	4.0	22.7	22.7	21.4	21.4	2.7	4.9
European Union	8.5	11.1	10.7	39.2	4.4	25.5	24.5	24.8	23.7	3.4	6.4

TABLE V – NUMBER OF NEW CANCER CASES ATTRIBUTABLE TO OVERWEIGHT AND OBESITY IN THE COUNTRIES OF THE EUROPEAN UNION AROUND 1995, BY CANCER SITE

Country	Breast women	Colon		Endometrium women	Prostate men	Kidney		Gallbladder		Total	
		Men	Women			Men	Women	Men	Women	Men	Women
Austria	260	240	200	290	110	130	90	60	80	530	930
Belgium	430	300	300	420	190	170	120	40	70	700	1,340
Denmark	140	160	110	170	50	80	50	20	20	320	490
Finland	210	120	120	260	120	110	90	50	40	400	730
France	1,840	1,760	1,440	1,680	850	900	410	210	360	3,720	5,730
Germany	3,340	2,950	3,020	2,920	1,390	2,080	1,210	1,520	1,230	7,940	11,720
Greece	300	170	170	250	70	140	70	20	30	400	820
Ireland	90	90	70	80	40	30	20	10	20	180	280
Italy	2,180	1,870	1,670	3,550	620	1,340	670	440	540	4,270	8,600
Luxembourg	10	10	10	20	10	<10	<10	<10	<10	20	50
The Netherlands	480	400	330	420	250	230	130	90	80	970	1,440
Portugal	280	290	260	430	90	100	60	30	60	510	1,080
Spain	1,080	990	1,050	1,660	320	470	280	230	570	2,020	4,640
Sweden	290	240	200	340	210	140	90	90	100	690	1,020
United Kingdom	1,950	1,560	1,490	1,760	680	700	440	180	250	3,120	5,890
European Union	12,870	11,150	10,460	14,230	4,990	6,640	3,740	3,010	3,450	25,790	44,750

Based on the estimated RR, the proportion of prostate cancers attributable to overweight and obesity among European men is 4% (Table IV). This corresponds to 5,000 new cases per year (Table V).

Endometrial cancer

Fourteen studies on endometrial cancer were included in the review;[1,33,58,93–103] 1 was conducted in China and the others in North America or Europe. All but 1[96] of the cohort studies[1,33,58,102] and all population-based case-control studies[93,95,97,99,100,101,103] showed a positive association between endometrial cancer and excess weight. Associations were stronger with overweight and obesity late in life[98] and for women with metastatic disease.[95] Besides BMI, measurements of waist-to-hip ratio and of skinfold have been used in studies of endometrial cancer,[99,100,102,103] also indicating a positive association. We considered age, social class, parity, use of oral contraceptives and hormone replacement therapy as the main potential confounders. Half of the selected studies adjusted only for age[33,58,93,94] or for no confounders.[1,95,102] Three studies adjusted for all of the major confounders.[97,98,103]

Only 4 studies provided enough information to be included in the meta-analysis[97,99–101] (Table IIE). The average increase in RR was 1.10 per unit of increase in BMI (95% CI 1.07–1.12) (Table IIE). All of these studies included incident cases, and models A and B were therefore identical. Only 1 study qualified for analysis C.[97] Restricting the analysis to this single study affected only the CI (RR 1.10, 95% CI 1.07–1.14).

The estimate obtained in analysis A/B implied an increase in risk by 59% for overweight women compared with normal weight and 152% for obese women (Table III). The proportion of endometrial cancers due to obesity in European women was estimated at 39% (Table IV), equivalent to 14,000 new cases per year (Table V).

Kidney cancer

We found 11 studies on kidney cancer eligible for review.[1,58,104–112] All were conducted in affluent countries. All but 2[108,112] included men and women. The case-control study was limited to cases of renal-cell cancer, the type responsible for 80% to 90% of all adult kidney neoplasms,[107] while 2 of the cohort studies included renal-cell and renal pelvic cancers.[1,58] A positive association with obesity was reported in all but 2 studies;[1,106] this was somewhat stronger in women than in men.[58,104,105,107–111] We considered age and smoking to be the major potential confounders in the association between obesity and kidney cancer. All but 2 studies[1,106] adjusted for age, but only 4 adjusted for smoking.[104,106,109,110]

In 2 of the studies, BMI was calculated as $kg/m^{1.5}$ for women.[107,110] To include these studies in the meta-analysis, we recalculated BMI (kg/m^2) by dividing the estimate ($kg/m^{1.5}$) by the square root of height, using a value of 1.64 m, based on the mean height for women in North America, the Netherlands and Sweden. Of the 7 studies included in the meta-analysis[104,105,107,109–112] (Table IIF), all but 1 provided separate results for men and women (contributing 13 degrees of freedom for the estimation of RR).

Overweight and obesity were positively associated with kidney cancer (RR = 1.06 per unit of increase in BMI, 95% CI 1.05–1.34) (Table IIF). Restricting the analyses to studies based only on incident cases[105,107,109,110,112] and further to studies that adjusted for age and smoking[109,110] changed the estimates only marginally. Models B and C gave the same estimates for the log-linear relationships between BMI and risk of kidney cancer, though fewer studies contributed to the second. We did not detect heterogeneity by sex: the results of model B in men and women estimated separately were 1.06 (95% CI 1.03–1.08) and 1.07 (95% CI 1.05–1.09), respectively.

Estimated RR corresponds to an increase in risk of 36% for an overweight person compared with one of normal weight and an increase of 84% for an obese person (Table III). In the European Union, about 25% of male cases and 24% of female cases of kidney cancer can be attributed to excess weight (Table IV). This corresponds to over 10,000 new cases of kidney cancer annually (Table V).

Gallbladder cancer

We found so few epidemiological studies of gallbladder cancer that eligibility criteria could not be applied. The 6 studies[1,58,113–116] are summarised in Table IIG. The results of these studies are conflicting. An excess of deaths from cancer of the gallbladder or biliary ducts was observed in women weighing 10% more than the average population, but no excess risk was observed in men.[1] Furthermore, no association was found for either sex in a Danish cohort study.[58] All but 1[113] of the case-control studies indicated an increased risk of gallbladder cancer with obesity. However, the association was limited to women in the large multi-centre study of Zatonski *et al*..[116] This was also the only study that controlled for the potential risk factors age, alcohol drinking, tobacco smoking and socio-demographic characteristics.

Only 1 study[115] provided sufficient information to estimate a dose-response relationship, and this was conducted in South America. The only data missing in the largest study[116] were the cut-points corresponding to the BMI quartiles that define exposure levels. We tested the extent to which different assumptions on the distribution of the BMI, within reasonable limits, would affect the estimated slope and found variations on the order of 1/1,000. We therefore included this study in our calculations, assuming as cut-points those given in the study of kidney cancer by Mellemgaard *et al.*,[110] which was conducted with similar methodology in the same populations. Data for men and women were included as independent observations. We found a positive association (RR = 1.06 per unit of increase in BMI, 95% CI 1.00–1.12). The results are presented in Table IIG.

The estimated association predicted 34% and 78% increases in risk for overweight and obese *vs.* normal subjects, respectively (Table III). As a result, 24% of these rare cancers are attributable to excess body mass in the European Union (Table IV), *i.e.,* 6,000 new cases per year (Table V).

All sites combined

The strongest relationships between excess weight and cancer risk were for cancers of the endometrium, kidney and gallbladder (Table III), giving correspondingly high attributable proportions: 2 of 5 endometrial cancer cases and 1 of 4 kidney and gallbladder cancers (Table IV). These are, however, relatively uncommon sites and, thus, add little to the total burden of disease (Table V). The largest number of attributable cases is for colon cancer, with 21,500 cases annually due to overweight and obesity, or 1.5% of the 1.5 million annual new cases in the European Union. Overall, excess body mass accounts for 5% of all cancers, 3% in men and 6% in women (Table VI), corresponding to 27,000 male and 45,000 female cancer cases yearly. Overweight accounts for a slightly higher proportion of cases among men, while cancer cases due to obesity are more common among women.

The greatest attributable proportion of cases, for women, is estimated in Spain and, for men, in Germany.

TABLE VI – PROPORTION OF CANCER CASES ATTRIBUTABLE TO OVERWEIGHT AND OBESITY IN THE EUROPEAN UNION, BY CANCER SITE

	Men		Women	
	Overweight[1]	Obese[2]	Overweight[1]	Obese[2]
Breast			4.1	4.5
Colon	6.9	4.2	5.0	5.7
Endometrium			17.2	22.0
Prostate	2.9	1.6		
Kidney	15.2	10.3	11.1	13.4
Gallbladder	14.7	10.1	10.7	13.0
All cancer sites	2.1	1.3	2.9	3.5

[1]Obese, BMI $\geq$ 30.–[2]Overweight, 25 $\leq$ BMI $<$ 30.

A clear gradient from north to south is observed for the male to female ratio of attributable cases. High body mass accounts for 3 times more cases in women than in men in Spain, Greece and Portugal, while in northern Europe, the ratio is $\leq$2, mainly because of the higher occurrence of tobacco-related cancers in men in northern Europe.

DISCUSSION

Our analysis indicates that each year about 34,800 new cases of cancer in the European Union are related to obesity and a further 37,000 cases to overweight. Most likely, these are conservative estimates if the association of BMI with several other cancer sites is confirmed. Our findings have considerable public health relevance since they suggest that it is possible to prevent an appreciable proportion of cancer cases by maintaining a healthy body weight. In terms of number of cases, reduction of body mass would have its greatest effects on endometrial, breast and colon cancers.

We quantified the proportion of cancers attributable to excess body mass for selected cancer sites in the European Union, following a systematic approach. For this purpose, we implicitly assumed that the associations considered were causal. The concept of causality in observational sciences has been thoroughly discussed in the epidemiological literature.[117–119] The assumption of causality is established based not only on epidemiological evidence but also on information from other domains, such as animal experiments and molecular biology.[120]

Walter[121,122] discussed the concept and interpretation of the attributable fraction. For a multifactorial disease such as cancer, the impact of a causal factor in determining the cancer burden in a given population might be modified by the prevalence of cofactors. Any intervention to reduce excess weight would entail the modification of nutritional habits towards a different composition of the habitual diet to reduced energy intake (increased consumption of vegetables at the expense of sources of protein, fat and carbohydrates) and increased physical exercise. The latter 2 may play independent roles in the causation of the same cancers, and the overall impact of interventions to reduce excess weight might therefore be greater than that estimated in our work.

We carried out these meta-analyses to obtain quantitative estimates of the strength of the associations considered; their statistical significance was, therefore, not a critical aspect of the evaluation. We tried to limit the impact of biases potentially affecting observational studies by selecting all those which satisfy *a priori* characteristics of study design so as to mimic the situation of pooled analyses of experimental studies. By selecting large studies we meant to reduce "publication" bias (failure to include negative studies never published because of their outcome). These take advantage of external funding and are therefore bound to report their results. The *(a priori)* limitations which we imposed in defining studies eligible for the analysis, therefore, were aimed at improving the validity of our results.

Conversely, an unwanted limitation is that not all published studies provide sufficient information to permit their inclusion in our analyses. This is a limitation always faced in meta-analyses

relying only on material as published. For each cancer site, several of the eligible studies could not be included in the meta-analysis due to at least 1 of the following conditions: use of measures of obesity other than BMI, missing RR or 95% CI. The effect of this forced selection on the point estimates of the slopes is unpredictable but certainly not biased by *a priori* hypotheses. One can instead affirm that their 95% CIs do not reflect the amount of information published and would have been narrower if all information could be exploited for the quantitative analyses. We estimated the RR in 3 models, with gradually increasing restrictions for inclusion criteria. For all of the 6 cancer sites studied, the RRs and 95% CIs thus obtained were virtually the same.

The cut-points of BMI which we adopted to define the population at risk are those recommended by WHO. These are based on evidence that mortality (all causes) increases significantly with BMI above 25 kg/m,^{2} which applies to several diseases common in Western countries.[19,22] Since the ultimate objective of this kind of exercise is to provide a basis for public health priorities, the definition of the "at-risk" population should be consistent with general guidelines.

We used non-national prevalence data obtained from 2 consistent sources[26,27] to improve comparability of the data from the different countries considered, possibly at the expense of representativeness. National estimates for the relevant period have been published for 3 countries. In the age range of the MONICA study, the prevalence of obesity in Germany in 1990[123] was similar to the figures we used. In the United Kingdom, national estimates of population excess weight (BMI >25 kg/m^2) in 1980 were greater than the MONICA figures by 7% and 11% in men and women, respectively.[124] In Swedish men, national estimates from 1988 to 1989[125] were 13% lower than the figures we used. There were no comparable data for Swedish women.

Overall, our results are in agreement with fractions attributable to obesity computed for the Nordic countries in a previous study.[126] Exceptions are estimates of endometrial and prostate cancers, which are lower in our results, and the attributable proportions of gallbladder cancers in women, which are higher. The differences for prostate cancer are explained by different RR values (1.12 in our study *vs.* 2.0). Other differences are therefore due to differences in the estimated prevalence of obesity. Our estimate of menopausal breast cancer attributable to overweight is in agreement with an estimate obtained from direct observation.[127]

We aimed at quantifying the magnitude of the problem of overweight as a basis of the potential of interventions to reduce cancer burden. Over 70,000 cancer cases in the European Union may be attributed to overweight and obesity, corresponding to 5% of all cancer cases. It is probably unrealistic to aim at eliminating completely this factor in Europe, where approximately 50% of the adult population is either overweight or obese; however, a substantial number of cancer cases could be avoided by halving that prevalence. Because excess weight is on the increase in most European countries,[128] adverse effects might therefore be even more pronounced in the future. Translation of the present findings into preventive strategies should become an important public health priority.

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