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Cancers attributable to overweight and obesity in Italy

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ABSTRACT

Background & aims: Overweight and obesity are associated with multiple cancers. We quantified the burden of cancer attributable to overweight and obesity in Italy.
Methods: We estimated sex- and cancer site-specific population attributable fractions (PAFs) combining relative risks (from recent meta-analyses) with national obesity prevalence data (from a large sample survey conducted in 2005, to account for a 15-year lag period). Using nationwide mortality statistics and cancer registries data, we estimated the number of cancer cases and deaths attributable to overweight and obesity in Italy in 2020, based on the counterfactual scenario of a body mass index < 25 kg/m^2.
Results: 3.6% of cancers in men and 4.0% in women in Italy were attributable to overweight and obesity, corresponding, respectively, to over 6900 and 7200 diagnoses in 2020. Attributable deaths were over 3600 in men and 2700 in women. PAFs (attributable cases) of overweight and obesity in men and women were, respectively, 38.1% (215 cases) and 21.8% (49 cases) for esophageal adenocarcinoma, 19.1% (1715 cases) and 14.5% (585 cases) for liver, 18.7% (1692 cases) and 16.7% (747 cases) for kidney, 13.7% (938 cases) and 10.1% (749 cases) for pancreatic, and 10.2% (2389 cases) and 3.4% (690 cases) for colorectal cancers. In women, PAFs were 22.3% (1859 cases) for endometrial and 5.7% (2556 cases) for post-menopausal breast cancer.
Conclusions: The cancer burden associated with overweight and obesity in Italy is considerable, but smaller compared to other high income countries, likely because of the lower prevalence of overweight and obesity in the Italian population.

1. Introduction

The prevalence of overweight and obesity has dramatically increased over the past 50 years globally, with significant public health burdens worldwide [1,2]. Such rise is mainly driven by changes in the global food system, enabling and promoting calorie-dense, nutrient-poor foods, alongside with increased sedentarism and decreased physical activity [3,4]. Based on global estimates from the World Health Organization (WHO), 1.9 billion (39%) adults were overweight and an additional 650 million (13%) were obese in 2016, with, however, wide regional variation [5]. The lowest obesity rates were observed in part of sub-Saharan Africa and in most countries of South Asia and South-Eastern Asia and the highest in the USA and in some West Asian and Northern African countries [6].

Overweight and obesity combined are considered indicative of excess body weight [7]. Excess body weight is associated with overall mortality and increased risk of multiple chronic conditions, including cardiovascular [5,8,9], metabolic [9–11] and musculoskeletal diseases [12,13], as well as selected types of cancers [14–16]. According to the World Cancer Research Fund (WCRF)/American Institute for Cancer

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Research (AICR) review, there is convincing evidence that excess body weight is directly related with endometrial, post-menopausal breast, liver, kidney, pancreatic, and colorectal cancers, and esophageal adenocarcinoma [17]. While the increase in risk for excess body weight is relatively modest for most cancer types, the corresponding cancer burden can be large given the high prevalence of overweight and obesity in several areas of the world. Excess weight was the third most important risk factor for risk-attributable cancer deaths and disability-adjusted life-years (DALYs), after smoking and alcohol, in a recent worldwide analysis [18].

In 2012, approximately 4% of all cancers worldwide were attributed to overweight and obesity [19,20], with analyses across macro-areas providing higher estimates for high than for low-income countries [21]. Although estimates of the cancer burden attributable to overweight and obesity have been provided for different countries [22–33], limited information is available for Italy [34], a country characterized by more favorable overweight and obesity rates and temporal trends compared with several other high income countries [35,36].

As part of a systematic assessment of the burden of cancer attributable to modifiable risk factors in Italy [37,38], the present study provides estimates of the national population attributable fraction (PAF) and the absolute number of cancer cases and deaths attributable to overweight and obesity in 2020.

2. Materials and methods

We considered cancer sites for which the WCRF/AICR review [17] reported a convincing evidence for association with excess body weight, i.e., adenocarcinoma of the oesophagus (International Classification of Disease-Oncology, third edition: C15), neoplasms of the colon and rectum (C18-C20), liver (C22), pancreas (C25), post-menopausal breast (C50), endometrium (C54), and kidney (C64).

For each cancer site, we computed the sex-specific PAFs using the Miettinen's formula for a polytomous exposure [39]:

$$PAF = \frac{\sum_{k=1}^{K}(RR_k - 1)\cdot Pr_k}{1 + \sum_{k=1}^{K}(RR_k - 1)\cdot Pr_k}$$

where RR_k and Pr_k are the relative risk (RR) and the prevalence in the population of the $k-$ th exposure level, respectively. We considered $K = 2$ exposure levels representing overweight (defined as body mass index, BMI, of 25–29.9 kg/m^2) and obesity (BMI$\geq$30 kg/m^2). The RRs and the corresponding 95% confidence intervals (CIs) of the associations between each cancer site and overweight and obesity were retrieved from recent meta-analyses [40–47], as reported in Table 1. When available, sex-specific meta-analytic estimates were extracted. The Italian prevalence of overweight and obesity in 2005 (Table 2) was obtained from a national sample survey (Multiscopo sulle famiglie: aspetti della vita quotidiana, Istituto Nazionale di Statistica, Istat, survey year 2005)[48], including approximately 24,000 individuals (11,516 men and 12,484 women). We extracted sex-specific prevalence of overweight and obesity for the adult population (i.e., ≥18 years). For women, we also extracted the prevalence in the post-menopausal period (i.e., ≥50 years) to estimate the PAF of post-menopausal breast cancer. We calculated the 95% CIs for the prevalence of overweight and obesity using the normal approximation of the binomial distribution [49]. To compute the 95% CIs for the PAFs, we performed 10,000 Monte Carlo simulations [50] using both the variability of the RRs and of the prevalence of overweight and obesity. Using the same approach, we computed PAFs and the corresponding 95% CIs according to age, based on sex- and age-specific prevalence data [48]. The number of cancer cases and deaths attributable to overweight and obesity were estimated by multiplying the PAFs with, respectively, the number of incident cases and deaths occurred in 2020 (i.e., assuming a latency of 15 years between overweight and obesity exposure and cancer diagnosis or mortality). Likewise, we calculated the 95% CIs for attributable cases and deaths applying the previous method to the 95% CI limits of the PAFs. The projected number of cancer cases in 2020 (based on data on diagnoses registered until 2016) was extracted from the Italian Association of Cancer Registries [51]; the number of cancer deaths occurred in 2020 was extracted from the national vital statistics on causes of death [52]. To estimate the number of cases and deaths subtypes not provided by these data sources, we used a previously developed distribution algorithm [37] or data retrieved from the 2020 GLOBOCAN database [53]. In particular, cases and deaths of adenocarcinoma of the esophagus were estimated as 33% of total esophageal cancer cases and deaths [37]; post-menopausal breast cancer cases were estimated by applying the proportion of breast cancer diagnoses over 50 years of age derived from 2020

Table 1
Relative risk (RR) and corresponding 95% confidence interval (CI) of overweight/obesity-related cancers according to overweight and obesity by sex.

Cancer site	Reference	Men RR (95% CI)	Women RR (95% CI)
Adenocarcinoma of the esophagus [C15]			
Overweight	Turati et al. [40]	2.13 (1.63–2.78)	1.59 (1.20–2.09)
Obesity		2.17 (1.56–3.01)	2.28 (1.64–3.18)
Colon and rectum [C18-C20]			
Overweight	Xue et al. [41]	1.17 (1.12–1.22)	1.07 (1.01–1.14)
Obesity		1.38 (1.32–1.44)	1.17 (1.06–1.30)
Liver [C22]			
Overweight	Sohn et al. [42]	1.36 (1.02–1.81)	1.36 (1.02–1.81)
Obesity		1.77 (1.56–2.01)	1.77 (1.56–2.01)
Pancreas [C25]			
Overweight	Alsamarrai et al. [43]	1.25 (1.10–1.42)	1.25 (1.10–1.42)
Obesity		1.48 (1.15–1.92)	1.48 (1.15–1.92)
Post-menopausal breast [C50]			
Overweight	Munsell et al. [44]	-	1.10 (1.06–1.13)
Obesity		-	1.18 (1.12–1.25)
Endometrium [C54]			
Overweight	Zhang et al. [45]	-	1.32 (1.16–1.50)
Obesity	Kalliala et al. [46]	-	3.10 (2.63–3.65)
Kidney [C64]			
Overweight	Liu et al. [47]	1.36 (1.22–1.53)	1.40 (1.30–1.50)
Obesity		1.71 (1.52–1.92)	1.99 (1.80–2.21)

Table 2
Prevalence and corresponding 95% confidence interval (CI) of overweight and obesity by sex. Italy, 2005.

Weight status	Reference	Prevalence (95% CI), %		
		Men, age≥ 18 years	Women, age≥ 18 years	Women, age≥ 50 years
Overweight	Multiscopo Istat 2005[48]	43.9 (42.9–44.8)	26.2 (25.5–27.0)	35.9 (34.7–37.1)
Obesity		10.2 (9.6–10.7)	9.7 (9.2–10.2)	14.8 (13.9–15.7)

Istat, National Institute of Statistics.

GLOBOCAN incidence estimates for Italy [53] to the total number of breast cancer diagnoses reported by the Italian Association of Cancer Registries [51]; and endometrial cancer deaths were obtained from 2020 GLOBOCAN deaths estimates for Italy [53].

All analyses were conducted in R version 4.2.0 (R Core Team, 2022).

3. Results

Table 3 reports the PAFs, the observed and attributable cancer cases, with the corresponding 95% CIs, due to overweight and obesity in Italy for each cancer site considered, according to sex. Among men, overweight and obesity were responsible for 6949 (95% CI: 4662–9275) cancer diagnoses in 2020 in Italy, corresponding to a PAF of all cancers of 3.6% (95% CI: 2.4%−4.8%). PAFs for specific cancers in men were: 38.1% (95% CI: 28.0%−47.8%) for adenocarcinoma of the esophagus, 19.1% (95% CI: 8.1%−30.4%) for liver, 18.7% (95% CI: 14.1%−23.4%) for kidney, 13.7% (95% CI: 7.8%−19.7%) for pancreatic, and 10.2% (95% CI: 8.4%−12.0%) for colorectal cancers. The number of attributable cases ranged from 215 (95% CI: 158–270) for adenocarcinoma of the esophagus to 2389 (95% CI: 1967–2810) for colorectal cancers.

Overweight and obesity accounted for 7235 incident cases (95% CI: 5194–9400) among women, corresponding to a PAF of 4.0% (95% CI: 2.9%−5.2%). The cancer-specific PAFs were 22.3% (95% CI: 18.3%−26.5%) for endometrial cancer, 21.8% (95% CI: 13.7%−30.4%) for adenocarcinoma of the esophagus, 16.7% (95% CI: 14.4%−19.1%) for kidney, 14.5% (95% CI: 7.3%−22.6%) for liver, 10.1% (95% CI: 5.7%−14.8%) for pancreatic, 5.7% (95% CI: 4.4%−7.1%) for post-menopausal breast, and 3.4% (95% CI: 1.5%−5.3%) for colorectal cancers. The highest absolute numbers resulted for post-menopausal breast and endometrial cancers, with 2556 (95% CI: 1973–3183) and 1859 (95% CI: 1525–2209) attributable cases, respectively. As in men, adenocarcinoma of the esophagus showed the lowest number of attributable cases (49; 95% CI: 31–69).

Fig. 1 shows the cancer-specific contribution to the total burden of overweight/obesity-related cancers. Among men, overweight contributed approximately twice (67.6%) as much as obesity (32.4%) to the total burden of cancers associated with excess body weight. In addition, 34.4% of cases attributable to overweight and obesity were from cancer of colon and rectum, and 24.7% and 24.4% were from cancers of liver and kidney, respectively. In women, overweight and obesity equally contributed to the total burden of attributable cancers (49.3% and 50.8%, respectively). Attributable cases of overweight and obesity were 35.3% and 25.7% from breast and endometrial cancers, respectively.

Sex-specific PAFs in strata of age are reported in Supplementary Table 1 and 2. For both men and women, the contribution of overweight and obesity to the cancer burden tended to increase with increasing age.

Attributable deaths are given in Supplementary Table 3. In men, greater numbers of attributable deaths were estimated for liver (1090;

Table 3
Population attributable fraction (PAF), observed and attributable cancer cases in 2020, and corresponding 95% confidence interval (CI) for overweight and obesity by sex in Italy.

Cancer site	Men			Women		
	PAF (95% CI), %	Observed cases, n	Attributable cases (95% CI), n	PAF (95% CI), %	Observed cases, n	Attributable cases (95% CI), n
Adenocarcinoma of the esophagus [C15]						
Overweight	30.7 (19.8–41.2)	564[a]	173 (112–232)	12.1 (4.6–20.5)	226[a]	27 (10–46)
Obesity	7.4 (3.5–12.2)		42 (20–69)	9.7 (4.9–15.5)		22 (11–35)
Overweight and obesity	38.1 (28.0–47.8)		215 (158–270)	21.8 (13.7–30.4)		49 (31–69)
Colon and rectum [C18-C20]						
Overweight	6.7 (4.9–8.6)	23420	1569 (1148–2014)	1.8 (0.2–3.4)	20282	365 (41–690)
Obesity	3.5 (2.9–4.0)		820 (679–937)	1.6 (0.5–2.7)		325 (101–548)
Overweight and obesity	10.2 (8.4–12.0)		2389 (1967–2810)	3.4 (1.5–5.3)		690 (304–1075)
Liver [C22]						
Overweight	12.8 (1.0–25.0)	8978	1149 (90–2244)	8.1 (0.6–16.6)	4034	327 (24–670)
Obesity	6.3 (4.5–8.4)		566 (404–754)	6.4 (4.6–8.3)		258 (186–335)
Overweight and obesity	19.1 (8.1–30.4)		1715 (727–2729)	14.5 (7.3–22.6)		585 (294–912)
Pancreas [C25]						
Overweight	9.5 (4.1–15.0)	6847	650 (281–1027)	5.9 (2.5–9.6)	7416	438 (185–712)
Obesity	4.2 (1.2–7.7)		288 (82–527)	4.2 (1.2–7.7)		311 (89–571)
Overweight and obesity	13.7 (7.8–19.7)		938 (534–1349)	10.1 (5.7–14.8)		749 (423–1098)
Post-menopausal breast [C50]						
Overweight	-	-	-	3.3 (2.2–4.4)	44835[b]	1480 (986–1973)
Obesity	-		-	2.5 (1.6–3.3)		1121 (717–1480)
Overweight and obesity	-		-	5.7 (4.4–7.1)		2556 (1973–3183)
Endometrium [C54]						
Overweight	-	-	-	6.5 (3.4–9.9)	8335	542 (283–825)
Obesity	-		-	15.8 (12.5–19.3)		1317 (1042–1609)
Overweight and obesity	-		-	22.3 (18.3–26.5)		1859 (1525–2209)
Kidney [C64]						
Overweight	12.8 (8.1–17.7)	9049	1158 (733–1602)	8.7 (6.8–10.8)	4472	389 (304–483)
Obesity	5.9 (4.3–7.5)		534 (389–679)	8.0 (6.4–9.6)		358 (286–429)
Overweight and obesity	18.7 (14.1–23.4)		1692 (1276–2117)	16.7 (14.4–19.1)		747 (644–854)
Overweight/obesity-related cancers[c]						
Overweight	9.6 (4.8–14.6)	48858	4699 (2364–7119)	4.0 (2.0–6.0)	89600	3568 (1833–5399)
Obesity	4.6 (3.2–6.1)		2250 (1574–2966)	4.1 (2.7–5.6)		3712 (2432–5007)
Overweight and obesity	14.2 (9.5–19.0)		6949 (4662–9275)	8.1 (5.8–10.5)		7235 (5194–9400)
All cancers[d]						
Overweight	2.4 (1.2–3.7)	194754	4699 (2364–7119)	2.0 (1.0–3.0)	181857	3568 (1833–5399)
Obesity	1.2 (0.8–1.5)		2250 (1574–2966)	2.0 (1.3–2.8)		3712 (2432–5007)
Overweight and obesity	3.6 (2.4–4.8)		6949 (4662–9275)	4.0 (2.9–5.2)		7235 (5194–9400)

[a]Adenocarcinoma of the esophagus were estimated as 33% of the total esophageal cancers according to previous defined algorithm; [b]Post-menopausal breast cancers were estimated applying the proportion of breast cancer diagnosis over 50 years of age derived from 2020 GLOBOCAN incidence estimates for Italy to the total breast cancer cases reported by the Italian Association of Cancer Registries; [c]Overweight/obesity-related cancers included adenocarcinoma of the esophagus, colon and rectum, liver, pancreas, post-menopausal breast, endometrium, and kidney cancers; [d]All cancers excluding non-melanoma skin cancer.

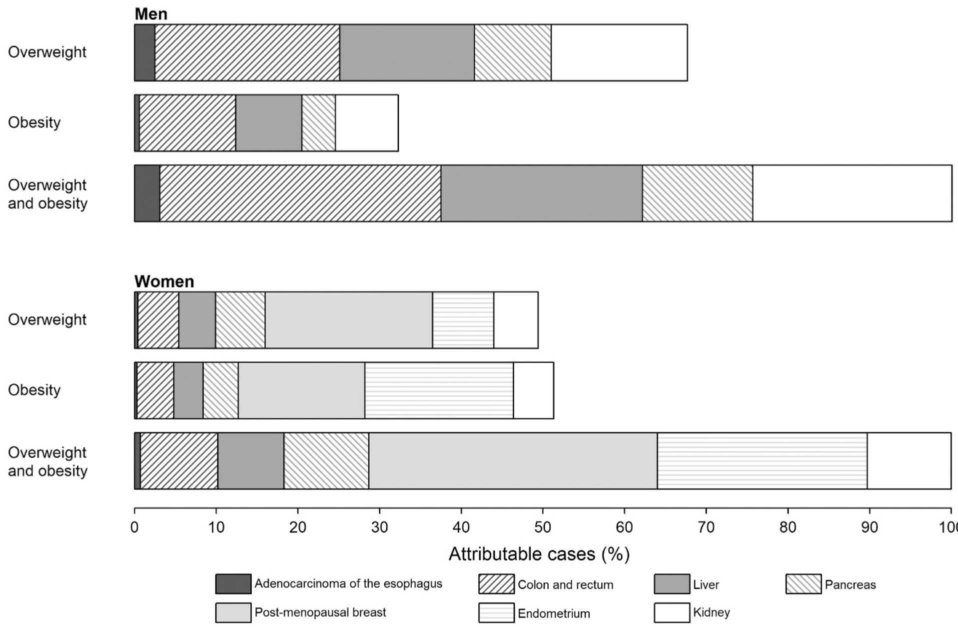

Fig. 1. Cancer-specific contribution to the total burden of overweight/obesity-related cancers. Italy, attributable cancer cases in 2020.

95% CI: 462–1735) and colorectal (1045; 95% CI: 861–1230) cancers; in women, the greater numbers of attributable deaths were from post-menopausal breast (693; 95% CI: 535–863), pancreatic (670; 95% CI: 378–982), and endometrial cancers (480; 95% CI: 394–570).

4. Discussion

This study provides national estimates of the cancer burden of overweight and obesity in Italy. We found that overweight and obesity were responsible, in 2020, for 3.6% of all cancers in men (~14% of overweight/obesity-related cancers), and 4.0% of all cancers in women (~8% of overweight/obesity-related cancers). Higher site-specific PAFs were estimated for men than women due to the higher prevalence of overweight in the former. Prevalence of obesity and RRs were, instead, relatively similar across sexes, with the exception of the RR of colorectal cancer, slightly higher in men than women. Overweight and obesity were, however, responsible for a somewhat higher number of cancers in women than men, essentially because of their role in endometrial and (post-menopausal) breast cancers [54].

Among the 7 cancer sites included in our assessment, esophageal adenocarcinoma and endometrial cancers had the highest PAFs (from 21% to 38%), as reported by other authors [23,24,27,28,55,56]. This reflects the stronger association of those cancer sites with excess body weight. PAFs ranging from 10% to 19% were estimated for kidney, liver and pancreatic cancers in both sexes and for colorectal cancer in men. The PAF for post-menopausal breast cancer appears low (5.7%), but the number of attributable cases was about 2550, which represents the highest burden of incident cases estimated. Together, post-menopausal breast and endometrial cancers accounted for more than 60% of the overweight-obesity related cancers in women. The endometrial cancer burden due to overweight and obesity in Italy is traditionally high [57], in part reflecting the low prevalence of HRT use in Italian women. In men, about a third of cases attributable to overweight and obesity were from colorectal cancer, and about a quarter from liver and kidney cancers each. The pattern of absolute numbers for cancer deaths was similar, with the greatest burden of deaths for liver and colorectal cancers in men, and cancers of the breast, pancreas, and endometrium in women.

A comparison of our results with those from other investigations is not simple since overweight/obesity rates have markedly changed in most countries over time and studies considered different timeframes for overweight/obesity data. In addition, the PAF for overall cancer depends on the types of cancers authors considered in their analysis. With this consideration in mind, the current PAFs of overall cancer in Italy appear lower than those reported for the UK (5.2% in men and 7.5% in women) [23], the USA (4.8% in men and 10.9% in women) [58], and Canada (4.9% in men and 6.5% in women) [25], comparable to those estimated for France (1.4% in men and 3.3% in women) [32], Brazil (2.2% in men and 4.3% in women) [24], Australia (2.5% in men and 4.6% in women) [28], and Denmark (2.9% in men and 3.7% in women) [33], and higher than estimates for Japan (0.8% in men and 1.6% in women) [22], Korea (1.5% in men and 2.2% in women) [29], and China (0.65% in men and women combined) [31] (Supplementary Table 4). This mostly reflects variation in the prevalence of overweight and obesity across populations.

In particular, a nearly 10-fold variation in obesity and overweight rates was observed across countries members of the Organisation for Economic Co-operation and Development (OECD). Around 2016, the USA had the highest prevalence of obesity (40%); the prevalence was also dramatically high, in Chile, Mexico, New Zealand and Hungary (between 30% and 35%) as well as in selected major Western Countries such as Canada, the UK and Germany (between 23% and 28%) [59]. Japan and Korea had the lowest obesity rates (<6%), followed by Italy (around 10%). Beyond OECD countries, relatively low obesity rates (5–10%) were observed for selected South Asia and South-Eastern Asia countries, China included [60]. While in most countries trends in overweight and obesity prevalence have been increasing over the last years, and are projected to increase further [61,62], surveys on the Italian population have indicated relatively stable trends across calendar years from the early 1990 s [35,36]. The more favorable figures for Italy compared to other high-income countries can be explained by the healthier dietary pattern [63,64], namely the Mediterranean diet, as well as the lack of a generalized increase in food portion sizes experienced by other high-income countries, including the USA [65] and some European countries [66]. The Mediterranean diet is characterized by consumption of whole or minimally processed foods, such as plant products, whole grains, fish and seafood, and olive oil, which may prevent the risk of excess body weight. Various epidemiological as well as intervention studies demonstrated potential benefits of the Mediterranean diet in obesity and associated metabolic conditions [67].

Other possible explanations for differences in PAFs across populations include different sources for RRs, and different time periods for overweigh and obesity prevalence and cancer data. In addition, PAF for overall cancer, calculated by adding-up site-specific attributable cases and then dividing by the total number of cases/deaths, depends on the cancers considered in the analysis, and by their relative frequency in the population. We considered cancers for which the WCRF/AICR reported a convincing association. Other studies defined different and/or expanded sets of cancer sites or types, considering, for example, also gallbladder [23–25,27,28,58], stomach (cardia) [23–25,27,58], ovarian [23–25,27,28,58], thyroid [23,24,27,58] and (advanced) prostate cancers [24,25,27], and/or multiple myeloma [23,24,27,58]; other studies, on the other hand, did not consider liver [22,28,29,32] or esophageal adenocarcinoma [22,29,68] in their evaluation.

Among study strengths, we used nationally representative data for the prevalence of overweight and obesity, extracted cancer-specific RRs from large meta-analyses, applied a standard methodology to derive PAFs and a Monte Carlo approach to incorporate uncertainties around the pointwise estimates of the PAFs and of the number of attributable cases and deaths. Also, we accounted for a reasonable 15-year induction period between the time of exposure and cancer occurrence. Since the prevalence of overweight and obesity in Italy has been relatively stable in the last decades (https://www.istat.it), assuming different, still reasonable, induction times ranging from 10 to 20 years would have resulted in similar PAFs estimates.

Our PAFs for overall cancer may be underestimated since we did not include in our assessment other cancer sites potentially associated to excess body weight. Further, in the national survey used as data source, BMI was derived from self-reported height and weight, with potential for underestimation of the prevalence of overweight and obesity, and hence of the PAFs. In addition, we applied the same RRs to incidence and mortality data, assuming no effect of overweight and obesity on cancer survival, and considered for cancer mortality the same time lag as for cancer incidence. We used the same RRs to compute PAFs according to age groups assuming the same strength of the associations between body fatness and cancer risk during the whole lifespan. Cancer mortality in 2020, and hence estimated attributable deaths, may be affected by COVID-19 pandemic; however, comparing national cancer mortality data in the years around 2020, we did not observe relevant temporal differences [52,53]. The issue is not relevant for incidence data, since we extracted cancer cases estimated to have occurred in 2020 based on available registered cancer data until 2016. Further, the method used to calculate the PAF estimates did not permit an evaluation of interactions between overweight/obesity and other risk factors for the considered cancers.

5. Conclusions

Overweight and obesity are associated with a considerable cancer burden in Italy, which however appears lower than that reported in other high-income countries. Still, our estimates indicate that implementing intervention to reduce excess body weight in the Italian population could decrease a substantial proportion of the cancer burden in Italy.

CRediT authorship contribution statement

Conceptualization: FT, MDM, CP, CLV; Coordination: CLV, FT, MDM; Investigation: all the authors; Methodology: FT, MDM, CP, CLV, PB; Statistical analysis: MDM, FT; Writing the original draft: FT; Funding: EN; Writing review and editing: all authors. All authors reviewed and approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.canep.2023.102468.

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