Lifestyle changes and reduction of colon cancer incidence in Europe: a scenario study of physical activity promotion and weight reduction

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Abstract

Background: Across Europe, there are over 300,000 new cases of colorectal cancer annually. Major risk factors include excess body weight (usually expressed by a high body mass index, BMI) and physical inactivity (PA). In this study we modeled the potential long-term effects on colon cancer incidence of changes in prevalence of excess body weight and physical inactivity in 7 European countries across Europe with adequate data.

Methods: We addressed the impact of interventions aimed at preventing weight gain and increasing physical activity on colon cancer incidence using the Prevent model as refined in the FP-6 Eurocadet project. Relative risk (RR) estimates were derived from meta-analyses; sex- and country-specific prevalences of BMI and PA were determined from survey data. Models were made for Czech Republic, Denmark, France, Latvia, the Netherlands, Spain and the United Kingdom.

Results: In a hypothetical scenario in which a whole population had obtained an ideal weight distribution in the year 2009, up to 11 new cases per 100,000 person-years would be avoided by 2040. The population attributable fractions (PAF) for excess weight were much higher for males (between 13.5% and 18.2%) than for females (2.3%-4.6%). In contrast, using the optimum scenario where everybody in Europe would adhere to the recommended guideline of at least 30 minutes of moderate PA 5 days per week, the PAFs for PA in various countries were substantially greater in women (4.4% - 21.2%) than in men (3.2%-11.6%).

Sensitivity analyses were performed assuming underreporting of BMI by using self-reports (difference of 5 and 0.8 percent-points in males and females, respectively), using different risk estimates (between 5.8 and 11.5 percent-points difference for BMI for men and women, respectively, and up to 11.6 percent-points difference for PA for women).

Interpretation: Changes in lifestyle can indeed result in large health benefits, including for colon cancer. Two interesting patterns emerged: for colon cancer, achieving optimum BMI levels in the population appears to offer greatest health benefits in population attributable fractions in males, while increased physical activity might offer the greatest fraction of avoidable cancers in females. These observations suggest a sex-specific strategy to colon cancer prevention.

Introduction

The incidence of colorectal cancer in Europe has increased since 1975, and comprised 13.6% of the estimated cancer burden by 2008 (1, 2). In 2004, colorectal cancer was the second most common incident cancer in Europe and also the second most common cause of cancer death (2, 3). An estimated 33% (females) to 53% (males) of European colorectal cancer cases could be avoided by reducing exposure to risk factors for colorectal cancer (4). Two important factors associated with an increased risk are physical inactivity and excess body weight (5, 6). These two factors were used in this study as a base for scenario studies investigating the long-term effects of changes in the prevalence of these risk factors on colon cancer incidence in seven European countries. These risk factors are inter-related in complex ways: in general physical inactivity increases with increasing body mass index (BMI) in a population; but while physical activity (PA) contributes to avoidance of weight gain, increased PA does not consistently result in weight reduction in overweight population (7). Because of this lack of a clear relationship, we treated these two risk factors separately for the purposes of this study.

The evidence of a beneficial effect of PA on cancer incidence is accumulating rapidly, and convincing results were reported for colon cancer (5, 8, 9). The reduction in colon cancer risk averages around 20%-30% comparing highest and lowest activity levels, an effect found consistently in different study designs and populations, also after correction for other risk factors such as dietary intake or body mass index (10, 11). There is a likely dose-response relation for colon cancer, with risk declining further at higher levels of PA (10, 12).

Another risk factor for colon cancer is excess weight, which is caused by a long-term imbalance between energy intake and energy expenditure. Dietary intake, physical activity and probably genetic make-up are important factors related to energy balance (5, 13). A recent study estimated that the population attributable risk of colon cancer due to overweight was 10.9% for European males and 2.6% for European females (13). Meta-analyses concluded that estimated risk ratios per 5 kg/m^2 increase in BMI varied between 1.16 and 1.28 for males and between 1.04-1.12 for females (10, 13).

Despite the benefits of PA and avoiding overweight, an increasing proportion of the European population has a BMI higher than 25 (13), and few Europeans are engaging in the amounts of PA recommended by current guidelines (at least 30 minutes of moderate intensity activity on 5 or more days a week)(14).

The EUROCADET (key DETerminants of future incidence of CAncer across EURope: impact of prevention) project assessed the impact of cancer prevention activities including interventions and legislations directed at life-style related risk factors on the future incidence of selected cancers across Europe ((2, 4, 13, 15-19). The objective of the current study was to demonstrate the impact of interventions to increase PA and/or reduce overweight on future colon cancer incidence up to 2040 in 7 European countries spread throughout the continent (Czech Republic, Denmark, France, Latvia, the Netherlands, Spain, and the United Kingdom), by means of a variety of scenarios, using the PREVENT modelling software (20). These scenarios illustrate priorities for further intervention development and research, and underpin European and national policies for cancer prevention.

Methods

Overview

We used modeling methods to make projections of future cancer incidence, where business as usual scenarios were compared with realistic and optimal intervention scenarios to obtain an indication of the long-term impact of interventions on cancer incidence.

The Prevent model

Future incidence was estimated using Prevent (19, 20). This program was adapted for the Eurocadet project to model future cancer incidence by implementation of lifestyle preventive strategies. Prevent calculated the percentages of potentially prevented cases under the scenario of interest as compared to the status quo scenario. If the scenario of interest is no exposure or exposure with minimum impact on risk this percentage is interpretable as the population attributable fraction (PAF) of BMI and PA respectively, on colon cancer incidence by the year 2040: they represent the numbers of cases that would be prevented had the population had the optimum BMI or PA and therefore the fraction of colon cancer cases attributable to these risk factors.

Three types of data are needed to run the model; demographic data (current and projected population sizes by age and sex), risk factor-related data (prevalence, changes in prevalence as a result of interventions and risk estimates), and disease incidence data (cancer rates and estimated annual percentage change to account for trends in disease incidence that are not associated with modeled risk factor data). The projected numbers of new cancer cases were computed based on the demographic data and under different scenarios of changes in the prevalence of risk factors. Results are projected rates and numbers with and without modeled interventions on risk factor prevalence.

Exposure: Body Mass Index and Physical Activity

The categorical distribution of BMI by country, sex, age category and calendar period was obtained from the sources described in table 1.

In all these countries, BMI was calculated based on self-reported height and weight. The prevalence of underweight, normal weight, overweight and obesity was fitted to a lognormal distribution in the same way as described in reference 19 (19).

The prevalence of moderate and vigorous intensity PA (e.g. cycling, brisk walking, doing sports) was obtained from the 2005 Eurobarometer surveys concerning social and political attitudes conducted on behalf of the European Commission in all member states of the European Union (http://ec.europa.eu/public_opinion/index_en.htm). PA was assessed using the International PA Questionnaire (IPAQ). The IPAQ measures the frequency, duration and level of intensity of PA in a 7-day period. Using individual-level data the weekly duration of PA in minutes was calculated by multiplying the numbers of days that these activities were undertaken by the estimated time per day spent doing it. This weekly duration, based on several questions with self-reported answers, occasionally resulted in very extreme numbers of hours of PA per day. Therefore, data were dichotomized to represent the prevalence of 'sufficient' PA (i.e., according to the guideline of 30 minutes per day for at least 5 days per week ~ 150 minutes/week) versus insufficient PA (less than 150 minutes per week). Table 1 summarizes the prevalence of moderate levels of PA by gender for the 6 countries included for these analyses.

Table 2 shows the mean BMI and prevalence of sufficient PA level according to sex for all age groups combined. At baseline, there were large variations in the distribution of these two variables.

<u>Incidence data: colon cancer</u>

National incidence rates for colon cancer (ICD-03 code: C18) by sex and 5-year age groups were retrieved from cancer registries. In France and Spain the average incidence rates of the available regional data were used as proxy for the national rates. For France data was only available for colorectal cancer, we calculated the rate of colon cancer as two thirds of the incidence of colorectal cancer. At baseline, there were large variations in levels of colon cancer incidence within Europe (table 2).

We applied country- and gender specific past trends of colon cancer using the corresponding EAPC (estimated annual percentage change) published recently (2).

Population projections

From Eurostat we obtained the size of the population on January 1, of the corresponding period of the latest available incidence data by 1-year age category and sex as well as forecasted population sizes for each year up to 2040 for the included countries by 5-year age categories and sex, using the medium national growth estimates.

Effect of physical activity and Body Mass Index on the incidence of colon cancer

Relative risks for PA and risk of colon cancer were estimated from a meta-analysis (11), which reported an association between leisure time PA and risk of colon cancer. Men and women who were sufficiently physically active had a pooled relative risk of developing colon cancer 0.78 and 0.71 compared to inactive men and women, respectively (results from cohort studies only).

Relative risk estimates for the relation between cancer and BMI were based on a recent meta-analysis of European studies, concluding the risk ratio for each increase of 5 kg/m^2 was 1,209 for men and 1,043 for women (13).

These findings were used as the relative risks and risk functions used in our modeling exercise (table 3). The relative risks and risk functions were assumed equal for all age groups and countries included in the study, and across time (21).

The effect of a risk factor exposure on cancer incidence may have a long latency time. Prevent accommodates this through two time lags: (1) the time that the risk remains unchanged after a decline in risk factor exposure (LAT) and (2) the period during which the changes in risk factor exposure gradually affects the risk of cancer, eventually reaching risk levels of the non-exposed (LAG) (19). For this study we used for BMI a LAT of 1 year and LAG of 9 years (based on (13)), and for PA a LAT of 5 years and a LAG of 15 years, in both cases LAG was modelled as a linearly declining risk.

We determined the theoretical minimum risk (TMR) exposure distribution as the counterfactual exposure distribution (22, 23). TMR were chosen to be BMI mean 21, standard deviation 1, and 30 minutes of PA per day for 5 days per week, as used by the Global Burden of Disease studies (23).

Intervention scenarios

Several intervention scenarios were applied to our analysis as follows:

1. USA: BMI increasing in the next 10 years in European countries as has been observed for the USA; 0.116 BMI point per year for males and 0.168 for females (24)
2. Optimum: All populations reaching optimum BMI levels (distribution of BMI with mean 21 and standard deviation 1) (23)
3. Netherlands: Reaching PA levels as obtained in the country with the highest prevalence of PA in this study: the Netherlands
4. Recommended: All population reaching recommended PA level (150 min/week) (23).

All interventions were modelled for the whole population, so for both sexes and all age groups.

The incidence level that was calculated with the intervention scenarios was compared to the reference scenarios, where BMI and PA levels remained at the level observed in the final year of observation. In most countries, levels of BMI were observed to increase constantly over the past decades. Therefore, the reference scenario of maintaining the status quo can be considered as the outcome of an effective intervention to avoid weight gain.

In calculating the future incidence we applied for both reference and intervention scenarios country- and sex-specific past trends of colon cancer using the corresponding EAPC (estimated annual percentage change) (2). In addition we also applied changes due to the influence of historically observed BMI levels.

Sensitivity analyses

The projections that PREVENT produces are dependent on the input data and assumptions of the model. We specified four sensitivity analyses to show the effects of changing a number of the base assumptions on the outcomes of the scenarios.

Sensitivity analysis 1: As it is known that self-reported BMI data are usually underreported (25, 26), we performed a sensitivity analysis for Denmark, based on a report from Sweden (26), where age- and sex-specific differences between mean self-reported BMI was compared with measured BMI. The same interventions were modelled with the 'corrected prevalence data'. The correction factors that were applied to the Danish data for all historical data up to and including the year 2005 are given in table 4.

Sensitivity analysis 2: To be able to show the influence of the precise RR estimates used in our modelling, we also performed sensitivity analyses using alternative RR estimates.
For PA, we decided to use for the sensitivity analyses of RR the results of a more recent meta analysis using only prospective observational studies (10). Summary RRs for high versus low levels of leisure time PA were 0.8 (95% CI 0.67-0.96) for males and 0.86 (95% CI 0.76-0.98) for females.

Sensitivity analysis 3: For the RRs on BMI we used the higher and lower limits of the 95% CI for the estimates used in this modelling exercise (table 2) (13). The applied risk ratio for each increase of 5 kg/m2 for the lower limits were 1.181 and 1.000 for men and women, respectively, and for the upper limits they were 1.234 and 1.101.

Sensitivity analysis 4: to show the effects of LAT and LAG estimates on the projections, we modelled the BMI-colon cancer relation as having a LAT of 0 years and a LAG of 5 years.

Results

The results of the scenario modeling on the projected age-standardized (European Standard Population) colon cancer incidence rates are described in figures 1 and 2 and table 5.

BMI scenarios

Under the scenario that overweight and obesity levels in European countries increase during the period 2009-2019 as they have been observed to increase in the United States in the past, the projected increase in rates in the selected countries compared to maintaining the status quo would vary between 1.7 (United Kingdom) and 2.8 more (Spain) cases per 100,000 person-years for males (figure 1, table 4). Corresponding increases for females would be between 0.1 (Czech Republic) and 0.6 more cases (the Netherlands) per 100,000 person-years. These increases in rates would translate to increases in numbers of new colon cancer cases between 0.7 and 3.8%.

Out of the newly diagnosed colon cancer cases that were projected to occur under the scenario where the BMI rates increase in the period 2009-2019 as they have been observed to increase in the USA, 0.7%-3.8% would not have occurred should the population have maintained BMI levels as in baseline. Much larger effects would be obtained if the population would on average lose weight: under the ideal circumstance that the whole population would obtain an ideal weight distribution, with a mean BMI of 21 with an SD of 1, between 0.6 (Czech Republic, females) and 11 (Spain, males) per 100,000 new colon cancer cases would be avoided by 2040 compared to maintaining the status quo at baseline, translating into a population attributable fraction (PAF) of overweight and BMI for colon cancer of 2.3% to 18%. PAFs for excess weight were much higher for males (between 13.5% and 18.2%) than females (2.3%-4.6%%)

Figure 2 shows the time-scale of the effects under the different scenarios, including sensitivity analyses 3 and 4. Effects of the 'optimum' intervention are seen rapidly after introduction in 2009, when the whole population distribution is modeled to abruptly shift to a BMI distribution with a mean of 21 and an sd of 1. Effects of the USA scenarios are seen on a longer time-frame, because changes are more gradual.

Numbers of incident cases increase rapidly, partly because of the 'autonomous' trends that were specified, but more importantly because of population ageing, resulting in large numbers of expected cases.

Physical activity scenarios

Should all countries adopt the PA levels as observed for the Netherlands, between 0.5 (Czech Republic, males) and 5.1 (Spain, females) per 100,000 colon cancer cases per 100,000 person-years, or up to 17.5% of new colon cancer cases might be prevented in 2040. Under the optimum scenario where everybody in Europe would adhere to the recommended guideline of at least 30 minutes of moderate to intense PA 5 days per week, between 1.5 (Czech Republic, males) to 6.4 (Spain, females) per 100,000 cases, or up to 21% of new colon cancer cases, could be prevented by 2040 (Table 4). PAFs for PA were between 3.2% and 12% for men and between 4.4% and 21% for women.

These results show that PAF for overweight and obesity in 2040 are consistently higher for European males than females, and highest for British males (18%). Conversely, PAF for PA show a more diffuse pattern by sex. Highest PAF for PA in 2040 was projected to be for Spanish females (21%).

Sensitivity analyses

The sensitivity analysis 1, performed for Denmark assuming underreporting of BMI because of using self-reports resulted in small differences for females, but large differences for males (table 5). The population attributable fraction (PAF) of obesity for colon cancer in the year 2040 would change from 13.8% to 18.7% for males and from 2.3% to 3.1% for females, if we assume underreporting as observed for Sweden (26).

Sensitivity analysis 2 using RR from a meta-analysis including only prospective observational studies for leisure-time PA and colon cancer risk showed a much larger impact on females than males, because the estimates for males were rather similar to the originally used RR. Differences in PAR were largest for the Spanish estimates compared to the 'recommended' scenario under the standard assumptions; 1,1 percent-point for males and 11.6 percent-points for women (table 6).

Sensitivity analysis 3, using the lower and upper limits of the 95% confidence intervals of the relative risks used for our BMI modeling illustrates the influence of effect size on the estimates: the PAR estimates differed up to 5.8 percent-points for men and up to 11.5 percent-points for women (table 6).

The results of sensitivity analysis 4 are shown in figure 2. Changing LAT from 1 to 0 years and LAG from 9 to 5 years for the BMI scenario causes changes in numbers of colon cancer cases to occur more rapidly, but hardly influences results on the long-term.

Discussion

Within Europe, there is a large variation in colon cancer incidence, but also in BMI and PA levels. Should interventions successfully achieve the optimum levels of BMI and PA in the populations, between 2.3% to 18.2% (optimum BMI) and 3.2% and 21.2% (optimum PA) of colon cancer cases might be avoided in the year 2040. Two interesting patterns emerged on modelling the potential benefits of increased PA and weight gain prevention across European populations with colon cancer as the malignancy of interest: improving BMI levels appears to offer greatest benefits for the male population; while increased PA might offer the greatest fraction of avoidable cancers among females. These findings are due to the fact that according to our input data, RR and prevalence of high BMI were highest for males and RR and prevalence of insufficient PA were highest for females. Although the modelled interventions are extreme scenarios, these observations suggest a sex-specific strategy to colon cancer prevention.
The results also show that, even though weigh management is clearly preferable over continuing weight gains, policy should really aim for weight loss among the overweight and obese. Even though optimum exposures will most likely never be achieved, it is possible to make important steps to improvement. Relatively high levels of PA are apparently possible to achieve, as the scenario from the Netherlands illustrated.

This is one of the first modelling exercises taking into account both BMI and PA for colon cancer and studying potential effects of different types of changes in risk factor exposure on a long term and in a population-based setting, offering useful insights for decision making in terms of primary prevention of colon cancer. Our outcomes show that even with somewhat extreme and overoptimistic assumptions the overall impact of risk factor modifications remains rather limited for this specific form of cancer. This illustrates the importance of additional secondary prevention by early detection for colon cancer, which could leave a substantially larger impact, even in the short run (27). However, since high BMI and low PA increase the risk of many chronic diseases, the overall public health benefits of interventions to reach optimum BMI and PA levels, will be much larger, particularly for cardiovascular diseases (23).

Our results are based on a number of assumptions, the most important ones being the risk function for BMI and the RR for PA and colon cancer risk, and representativeness of prevalence data for the different countries included in this modeling exercise.

Risk relations and included risk factors

The literature is quite consistent in concluding that there is an association between PA and BMI and colon cancer risk. The precise size of this association however, varies between studies. We performed sensitivity analyses with other values for the relative risk function and RRs to verify the extent to which this influences results, which turned out to be quite substantial (up to 11-12 percent-points difference) for the countries with the most extreme prevalence data and with the most extreme RR estimates (sensitivity analyses 2 and 3).

Colon cancer risk was modeled to be the effect of changes in PA or BMI, no other risk factors were taken explicitly into account. Colon cancer incidence levels will be influenced by (a.) risk factors for colon cancer such as PA and BMI as well as for example consumption of red meat and alcohol (5) (b.) genetic susceptibility of the populations and (c.) levels of screening for colorectal cancer in the population. In our analyses, we assumed that the changes in colon cancer incidence over time caused by these factors would be represented in the estimated annual percentage change.

In our scenarios the effects of PA and BMI were modeled independently, whereas they are likely to be interrelated. However, the few available results of long-term PA interventions generally show very little to virtually no significant difference in weight between the intervention and control groups and no dose-response relationships were observed (28, 29). A recent Cochrane review summarizing results of two studies observed a significant difference in weight change (mean difference -2.03 kg) and BMI change (mean difference -0.73 BMI points) between an exercise intervention group and a reference group (30). A recent large prospective cohort study illustrated that for with overweight or obesity, PA was not related to weight loss (31). Therefore, we do not believe that adding a potential effect of PA on BMI would have substantially influenced our results, since those potential effects would be absent or very small.

Prevalence data

Important input data for these models are the prevalence data of the risk factors in the different countries. These were based on samples of the population and may not always represent the true prevalence in a given population. In these population-samples, self-reported height and weight were used, which are known to give underestimates of the true BMI, therefore the potential reduction in incidence might be larger, as shown in the results of sensitivity analysis 1 (26, 32). Levels of PA were derived from the EUROBAROMETER survey, collected in a standardized manner. Reported prevalences of PA seemed rather high, and may possibly be a result of overestimating one's PA and socially desirable answers. However, data from the limited number of other sources reporting PA levels (e.g. Statistics Netherlands) also generally show high prevalences, reflecting either real high prevalences of PA or problems in accurately measuring PA, also indicating that the room for improving PA is probably larger than modeled in our scenarios.

<u>LAT and LAG</u>

The choices of the LAT and LAG times used for these modeling exercises have been rather arbitrary, since very little information on these issues is available from literature. For obesity and colon cancer we used the same estimate for total 'lag-time' as a previous paper (13) and translated this into LAT=1 and LAG=9 years (13). The real LAT and LAG are determined by the stage at which the risk factors act (development of adenomas, progression of adenomas, transition from adenomas to colon cancer), but the exact mechanisms by which BMI and PA act on colon cancer risk are debated (10, 33, 34). However, results from sensitivity analysis 4, changing the levels of LAT and LAG, show that these choices mainly influence results in the first years after the risk factor change, and therefore hardly influence outcomes for 2040 (figure 1). For projections on shorter terms, these assumptions become more important.

Another issue that is of importance in interpreting these results is how the changes in BMI and/or PA could be achieved in practical terms.

Considering the observed increases in obesity prevalence in many countries over the past decades, combined with the difficulties in finding effective measures to combat obesity (18), particularly at population level, maintaining the current weight distribution of the population would be already a good achievement. However, current evidence of efficacy of obesity prevention interventions is limited. A review on the evidence of interventions to avoid weight gain identified some studies with a positive impact on body mass index or weight status (18). However, there was too much heterogeneity in terms of study design, theoretical underpinning and target population to draw firm conclusions about which intervention approaches were more effective than others.

Other possibilities to influence population BMI include policy interventions that affect the population at large, such as price policies, although empirical evidence for food price sensitivity of weight outcomes indicates that small taxes or subsidies are unlikely to influence population overweight and obesity levels (35). Stronger pricing interventions might particularly influence prevalence of overweight of children and adolescents, people of lower socio-economic groups and those most at risk for overweight (35). A modeling study on effects of different taxing methods on unhealthy and healthy food items concluded that numbers of deaths were reduced only when increased taxes for unhealthy food were combined with subsidies for healthy food, although only a minor proportion of these deaths would be obesity-related colon cancer (35).

The high prevalence of PA in the Netherlands is partly related to the high frequency of bike-use, not only for recreational purposes, but also as a means of transportation to work and other activities. When adequate cycling infra-structure would be implemented across Europe, it is likely that more people would cycle. A large change in the city infrastructure that promotes walking and cycling has been reported in Bogotá, Colombia where an increase of 291 km bicycle route within 1992 and 2003 has resulted in an increased of share transportation by bicycle from 0.58% to 4.4% (36). However, this involved quite radical culture change in many countries, which will not be easy to achieve. Even in Bogotá, the level of cycling did not reach that of the Netherlands. Part of this is probably because the situation in the Netherlands is ideal for biking: it is flat and there are separate bicycle lanes practically everywhere in the country. Generally, distances are relatively short. Car-drivers are used to bicyclists, making the situation in the traffic safer. Over the past years, we have seen a rise in the number of city-bike plans in many countries, illustrating the potential of increasing bike use (37).

There are of course many different types of PA, and hence many possibilities for interventions. In the Netherlands, walking also contributes a marked amount of time of the total physical activity (38). Several studies have been investigated environmental characteristics that are associated with (not) walking, and have found quite consistently that environments that are perceived as more aesthetic/enjoyable, convenient and safe, combined with good access to facilities promotes walking activities (37). Another potentially important source of PA within daily life activities is stair climbing. Several studies have assessed interventions to increase stair climbing, mostly comparing situations with and without motivational signs that were placed besides escalators with adjacent stairs. These 'point of choice' prompts generally appeared to be effective, with increases in stair climbing varying between 5.8%-61%, depending on the setting of the intervention (volume of people passing by the stairs, type of motivational sign, etc) (38-43). However, all of these interventions probably result in small increases in PA. A combination of interventions at policy level, in the living environment and individual level is needed to substantially increase PA levels on a population level.

In summary, changes in levels of PA and/or mean levels of overweight in the selected European populations would result in quite substantial effects on future colon cancer incidence rates. In terms of avoided number of cases, however, these effects are even more substantial, particularly under the more extreme interventions, where the whole population would adhere to recommendations by the WHO: then up to 18.2% (BMI, males) or 21.2% (PA, females) of colon cancer cases would be avoided under the assumptions of these modeling exercises. Interventions on BMI would have larger impact for European males, and interventions on PA on females.

Modifying lifestyle is difficult and the scenarios modeled in this paper were hypothetical. Before policy-makers act and implement prevention activities aiming to reduce cancer through lifestyle changes, sound evidence on the effectivity of the interventions should be sought. Yet, the example of the scenario of PA as in the Netherlands demonstrates that substantial benefit from increasing PA to a level that has been demonstrated possible to achieve in other country, whereas the example of the scenario where BMI increases as it has in the past in the USA underlines the importance of stopping and reversing the ongoing increase in overweight and obesity prevalence.

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Table 1: Sources and details of Body Mass Index data used as base for the modeling in addition to the WHO Global Database (44)

Country	Data source(s), numbers refer to numbers in reference list	Age groups (years)	Time period
Czech Republic	WHO Global database only (44)	All ages combined	1990-2002
Denmark	Danish national Institute of Public Health	0-24; 25-44; 45-66; 67+	1990-2005
France	specific French studies (45, 46)	0-29; 30-39; 40-49; 50-59; 60+	1990-2006
Latvia	Latvian National Public Health Institute combined survey in the Baltic countries (47)	0-24; 25-34; 35-44; 45-54; 55+	1995-2006
The Netherlands	Statistics Netherlands (48)	0-24; 25-34; 35-44; 45-54; 55-64; 65-74; 75+	1999-2007
Spain	Spanish Surveys (49 1997, 2001, 2003, 2006 #41 1997, 2001, 2003, 2006 #41)	0-24; 25-34; 35-44; 45-54; 55-64; 65-74; 75+	1990-2006
United Kingdom	Health Survey for England (England and Wales)	0-24; 25-34; 35-44; 45-54; 55-64; 65-74; 75+	1992-2007

Table 2: Colon cancer incidence and risk factor prevalence by sex in selected countries

Country/ gender	Data-source incidence data	Projected Colon cancer Incidence *(ESR) in 2009	EAPC Colon (year of observation) *	Prevalence fulfilling moderate PA norm (>150 min per week) in 2005	Mean BMI (year of observation)
MALES					
Czech Republic	NCR, 2003	29	1.1 (1994-2004)	84%	26 (2002)
Denmark	NCR, 2004	39.6	1.0 (1994-2003)	78%	25 (2005)
France	RCR, 2000	42.2	0.7 (1995-2000)	65%	25 (2006)
Latvia	NCR, 2005	29.8	1.9 (1993-2004)	82%	25 (2006)
Netherlands	NCR, 2005	43	0.9 (1994-2003)	88%	25 (2007)
Spain	RCR, 2002	46.9	4.4 (1994-1997,2000)	53%	26 (2006)
United Kingdom	NCR, 2005	31.5	-0.2 (1995-2004)	66%	27(2007)
FEMALES					
Czech Republic	NCR, 2003	13.2	0.3 (1994-2004)	70%	25 (2002)
Denmark	NCR, 2004	31.3	0.2 (1994-2003)	70%	24 (2005)
France	RCR, 2000	25.4	0.4 (1995-2000)	49%	24 (2006)
Latvia	NCR, 2005	18.9	2.7 (1993-2004)	70%	25 (2006)
Netherlands	NCR, 2005	30.5	0.8 (1994-2003)	89%	24 (2007)
Spain	RCR, 2002	29.3	3.3 (1994-1997,2000)	35%	25 (2006)
United Kingdom	NCR, 2005	22.2	-0.5 (1995-2004)	49%	26 (2007)

NCR National Cancer Registry or combined regional registries covering whole country
RCR Regional cancer registries
* Derived from Karim-Kos et al EJC 2008 (2).

Table 3: Risk estimates and theoretical minimum risk (TMR) distribution for physical activity (PA) and Body Mass Index (BMI)

	Risk function	**TMR**
Physical activity, estimates from (11)	Relative Risk for colon cancer for insufficient PA versus sufficient PA Males: RR=1.28; females RR=1.41	Sufficient PA > 150 min/week
Body Mass Index, estimates from (13)	Relative risk for each increase of 5 kg/m2 Males: 1.21 (95% CI 1.18-1.23) Females: 1.04 (95% CI 1.00-1.10)	Mean = 21, SD=1

Table 4: Correction factors applied to mean self-reported Body Mass Index (BMI) levels in Denmark, for sensitivity analysis 1

Age groups	BMI points added to the mean (based on (26))	
	Males	Females
16-24 years	0.40	0.70
25-44 years	0.40	0.68
45-66 years	0.63	0.77
67-81 years	0.87	1.33

Tabel 5: Results of the scenarios for colon cancer 2040. Differences in rates and numbers

	Differences* in European standardized incidence rates, 2040								**Differences** in numbers of incident cases, 2040**							
Risk factor	BMI				PA				BMI				PA			
Scenario	USA		Optimum		Netherlands		Recommended		USA		Optimum		Netherlands		Recommended	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Czech Republic	+1.8	+0.1	-5.5	-0.6	-0.5	-0.9	-1.5	-1.6	3.6%	1.0%	-13.5%	-2.9%	-1.2%	-7.1%	-4.3%	-11.1%
Denmark	+2.4	+0.4	-7.5	-0.9	-1.3	-2.1	-2.5	-3.5	3.7%	1.0%	-13.8%	-2.3%	-2.7%	-8.9%	-5.8%	-11.0%
France	+2.5	+0.4	-8.8	-0.9	-2.7	-3.6	-4.1	-4.5	3.7%	1.1%	-15.8%	-2.9%	-6.0%	-13.4%	-8.9%	-17.4%
Latvia	+2.1	+0.5	-6.9	-1.5	-0.6	-1.8	-1.9	-2.9	3.5%	1.1%	-14.6%	-4.6%	-1.6%	-6.7%	-4.7%	-10.9%
Netherlands	+2.7	+0.6	-8.1	-1.1	-	-	-1.7	-1.5	3.7%	1.1%	-13.8%	-2.9%	-	-	-3.2%	-4.4%
Spain	+2.8	+0.3	-11.0	-1.4	-4.6	-5.1	-6.1	-6.4	3.8%	0.7%	-16.9%	-3.8%	-8.7%	-17.5%	-11.6%	-21.2%
UK	+1.7	+0.5	-7.1	-1.0	-1.7	-2.8	-2.6	-3.7	3.7%	1.1%	-18.2%	-4.2%	-5.8%	-13.6%	-8.7%	-17.4%

Scenarios:
- USA: BMI increase as in the USA: 0.116 BMI point per year for males and 0.168 for females
- Optimum: Average BMI 21 with standard deviation 1
- Netherlands: Prevalence of sufficient PA as observed in the Netherlands, 88% for males and 89% for females
- Recommended: All Europeans have at least 2.5 hours of physical activity per week

Abbreviations:
BMI: Body Mass Index, PA: Physical activity, M: male, F: female
* Absolute difference in rate: a value of -1,2 means 1,2 per 100,000 person-years less cases in the intervention scenario
** Relative difference in number: out of the reference scenario, x% would be avoided under the scenarios

Table 6: Results of sensitivity analysis assuming underreporting in self-reported Body Mass Index for Denmark (sensitivity analysis 1) and different Relative Risk estimates for physical activity for all countries (sensitivity analysis 2)

	Differences in European standardized incidence rates, 2040*				**Differences in numbers of incident cases, 2040****			
Scenario	**BMI USA**		**BMI optimum**		**BMI USA**		**BMI optimum**	
	M	F	M	F	M	F	M	F
Original DK	+2.4	+0.4	-7.5	-0.9	+3.7%	+1.0%	-13.8%	-2.3%
Sensitivity DK	+2.2	+0.4	-8.5	-1.2	+3.2%	+1.0%	-18.7%	-3.1%
Scenario	**PA NL**		**PA recommended**		**PA NL**		**PA recommended**	
	M	F	M	F	M	F	M	F
Czech Republic	-0.4	-0.5	-1.3	-0.7	-1.0%	-3.0%	-3.8%	-4.7%
Denmark	-1.1	-0.9	-2.3	-1.4	-2.4%	-5.2%	-5.2%	-4.7%
France	-2.5	-1.5	-3.7	-1.9	-5.4%	-5.9%	-8.0%	-7.7%
Latvia	-0.6	-0.8	-1.6	-1.2	-1.5%	-2.9%	-4.2%	-4.5%
Netherlands	-	-	-1.5	-0.7	-	-	-2.8%	-1.8%
Spain	-4.1	-2.3	-5.5	-2.8	-7.9%	-8.0%	-10.5%	-9.6%
UK	-1.6	-1.2	-2.3	-1.6	-5.2%	-6.0%	-7.9%	-7.7%

Scenarios:
- USA: BMI increase as in the USA: 0.116 BMI point per year for males and 0.168 for females
- Optimum: Average BMI 21 with standard deviation 1
- Netherlands: Prevalence of sufficient PA as observed in the Netherlands, 88% for males and 89% for females
- Recommended: All Europeans have at least 2.5 hours of physical activity per week

Abbreviations:
BMI: Body Mass Index, PA: Physical activity, DK: Denmark, M: male, F: female
* (Absolute) difference in rate: a value of -1,2 means 1,2 per 100,000 person-years less cases in the intervention scenario
** (Relative) difference in number: out of the reference scenario, x% would be avoided under the scenarios

Table 7: Results sensitivity analysis 3 using lower/upper limits of Confidence Interval for Relative Risk for Body Mass Index and Colon cancer

	Differences in European standardized incidence rates, 2040*				**Differences in numbers of incident cases, 2040****			
Scenario	USA 95%CI		Optimum 95%CI		USA 95%CI		Optimum 95%CI	
	M	F	M	F	M	F	M	F
Czech Republic	1.5; 2.1	0; 0.6	-6.1; -4.9	-1.1; 0	3.2%; 4.0%	0%; 2.6%	-17.5%; -13.5%	-7.1%; 0%
Denmark	2.1; 2.8	0; 1.2	-8.3; -6.7	-2.2; 0	3.2%; 4.1%	0%; 2.4%	-18.0%; -13.9%	-5.7%; 0%
France	2.2; 2.8	0; 0.9	-9.7; -7.7	-2.2; 0	3.3%; 4.1%	0%; 2.5%	-21.0%; -16.2%	-7.1%; 0%
Latvia	1.7; 2.2	0; 1.1	-7.7; -6.2	-3.3; 0	3.1%; 3.9%	0%; 2.7%	-19.2%; -14.8%	-11.5%; 0%
Netherlands	2.3; 3.0	0; 1.3	-8.9; -7.2	-2.7; 0	3.2%; 4.1%	0%; 2.6%	-18.0%; -13.9%	-7.1%; 0%
Spain	2.6; 3.3	0; 1.1	-12.2; -9.9	-3.2; 0	3.3%; 4.2%	0%; 2.7%	-22.8%; -17.6%	-9.5%; 0%
UK	1.5; 2.0	0; 0.9	-7.8; -6.4	-2.4; 0	3.3%; 4.1%	0%; 2.6%	-25.1%; -19.3%	-10.4%; 0%

Scenarios:
- USA: BMI increase as in the USA: 0.116 BMI point per year for males and 0.168 for females
- Optimum: Average BMI 21 with standard deviation 1

Abbreviations:
BMI: Body Mass Index, 95%CI: Upper and lower bound of 95% confidence interval, M: male, F: female
* Absolute difference in rate: a value of -1,2 means 1,2 per 100,000 person-years less cases in the intervention scenario
** Relative difference in number: out of the reference scenario, x% would be avoided under the scenarios

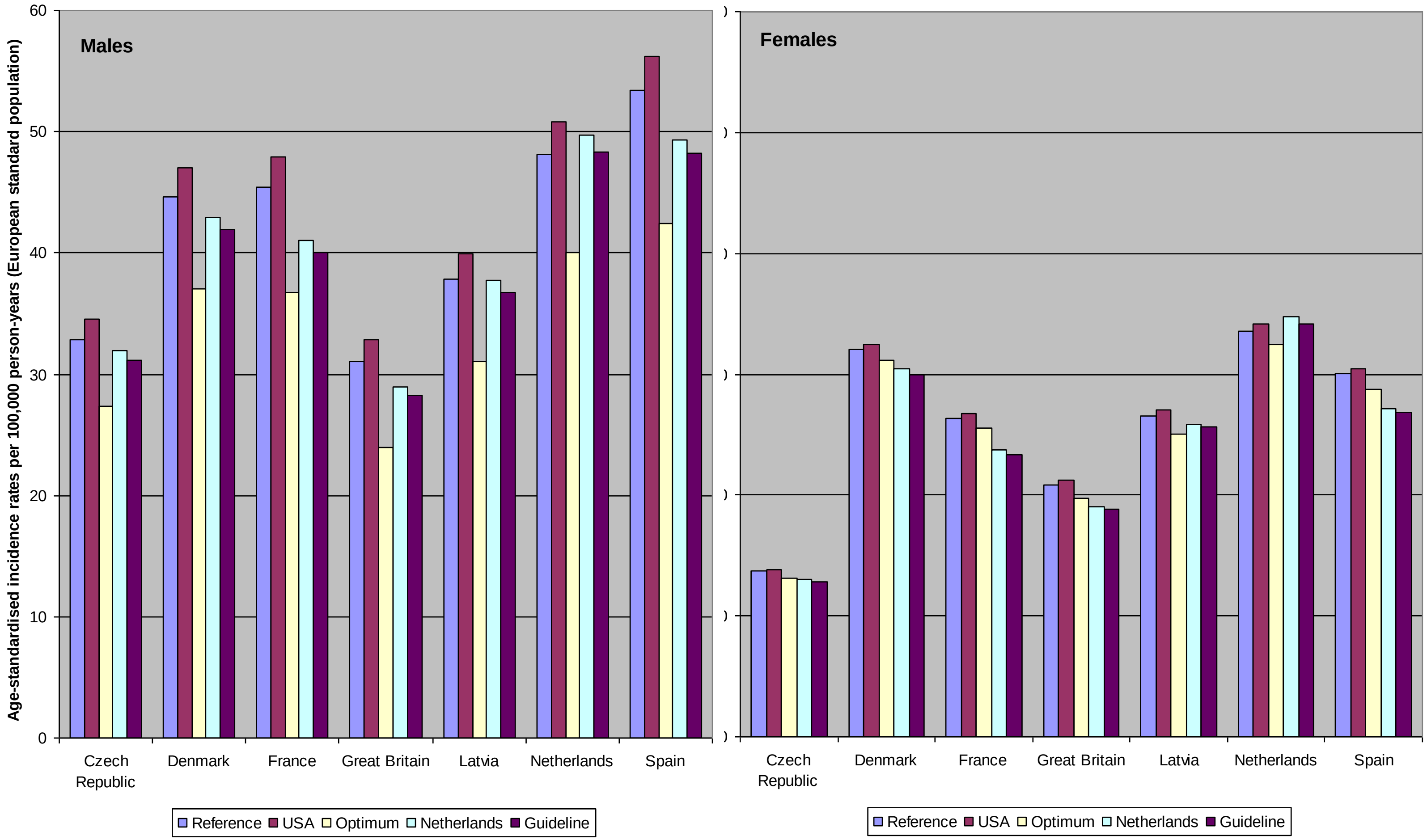

Figure 1: Projected age-standardised incidence rates in the year 2040 under the various scenarios in the different countries, by sex. Reference = maintaning status quo, USA = BMI increases as in USA, Optimum = all population reaching optimum BMI levels. Netherlands = PA levels as observed in the Netherlands, Guideline = PA levels as recommended by WHO

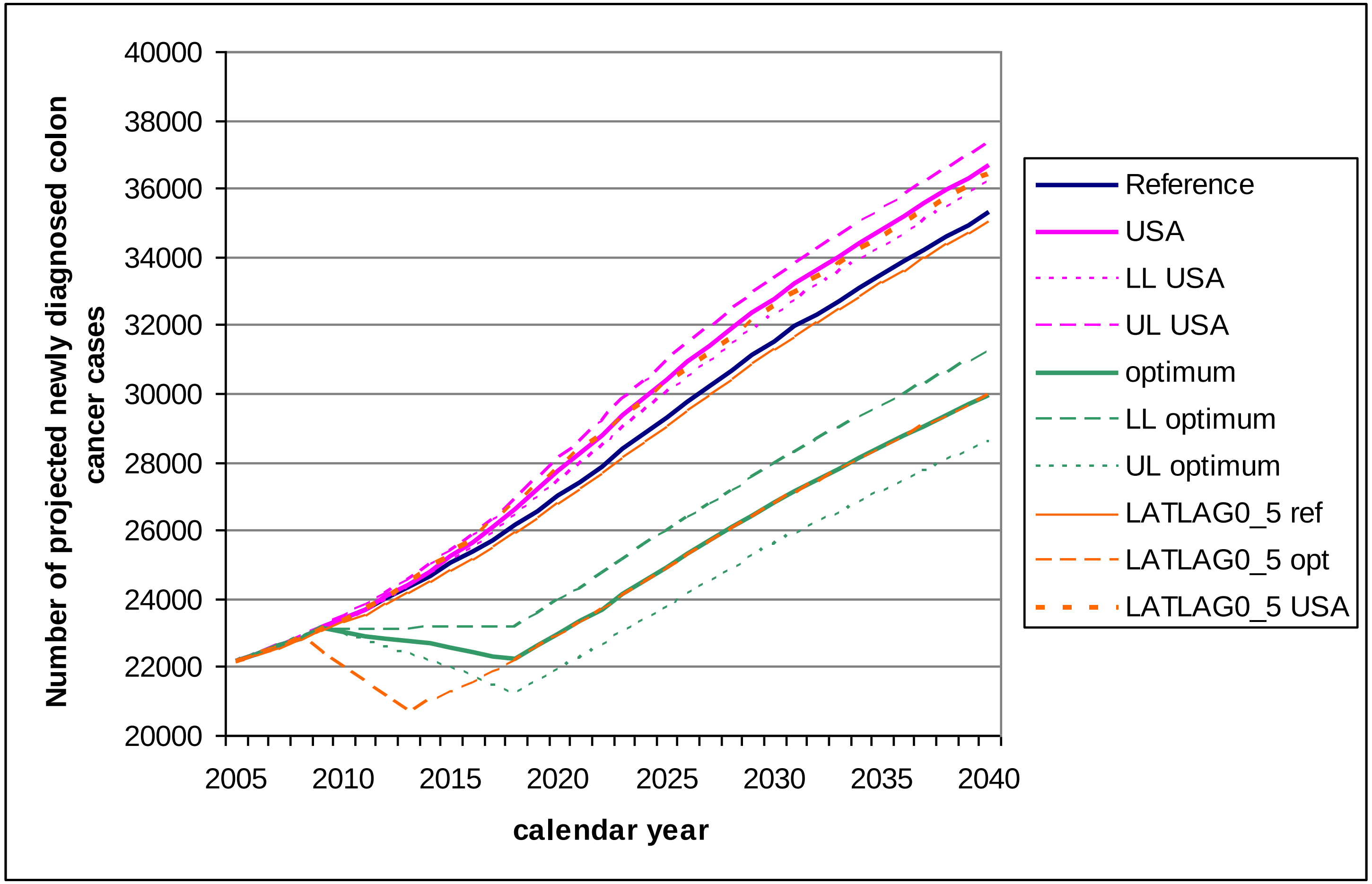

Figure 2: Outcomes of Prevent for the BMI-colon cancer modelling for the UK, under various scenarios and assumptions. Results for both sexes combined. Reference = maintaining status quo, USA = BMI increases as in USA, Optimum = all population reaching optimum BMI levels, LL and UL USA and optimum: using lower and upper limits for males and females (sensitivity analysis 3), LATLAG0_5 reference, optimum and USA: using standard modelling parameters but with LAT=0 and LAG=5 years (sensitivity analysis 4).