Food and Chemical Toxicology 130 (2019) 174–186

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Estimation of the burden of disease attributable to red meat consumption in France: Influence on colorectal cancer and cardiovascular diseases

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Keywords:
Risk assessment
Probabilistic model
Second order Monte Carlo simulation
DALY
Public health

A B S T R A C T

The consumption of red meat has been associated with colorectal cancer (CRC) and cardiovascular disease (CVD) worldwide. The objective of this study was to assess quantitatively the burden of disease of CRC and CVD due to the consumption of red meat in France. A probabilistic risk assessment model quantifying the risk, deaths and disability adjusted life years (DALY) of both outcomes was built. In the model, uncertainty and variability were propagated separately. The model used data on current CRC and CVD incidence and red meat consumption in France, as well as dose-response from epidemiological studies. Results were given by age class and gender. A total of 19 [95% CI = 8–33] DALY per 100,000 people per year for CRC associated with red meat consumption was estimated. For CVD, 21 [95% CI = 12–32] DALY per 100,000 people per year was estimated. The uncertainty was mainly due to the dose-response, as revealed by a sensitivity analysis. A scenario analysis, performed on red meat intake, highlighted that consumption of less than 65 g per day could limit the risk of CRC and CVD in the most affected sub-populations.

1. Introduction

Quantifying the impact of dietary habits on human health is essential for decision-making in preventive medicine (Karp et al., 2016). Diet is a key determinant of health status: it has been considered as one of the major factors in reducing the burden of disease (GBD 2017 Risk Factor Collaborators, 2018; Wolk, 2017). For instance, in Europe, a diet high in saturated fat was responsible for 1.1% of the overall burden of disease. In the USA, 35% of the total deaths resulting from cancer was estimated to be attributable to diet (food and drink), excepting alcohol (Pomerleau et al., 2003).

Since 1990, the Global Burden of Disease (GBD) study, supported by the World Health Organization, has estimated the health effects of major diseases, injury and risk factors with the Disability Adjusted Life Years (DALY) metric, which takes into account mortality and morbidity. This metric expresses the number of years of life lost (YLL) from premature death and the number of years lived with disability (YLD) (WHO, no date). In addition, by quantifying the impact of disease, the burden of disease helps in formulating risk-mitigating strategies: several consumption patterns could be evaluated and compared by a scenario analysis.

The estimation of the burden of disease is also used in risk–benefit assessments of food to quantitatively compare different health impacts associated with food consumption in a targeted population. This has been done in several studies (Berjia et al., 2014; Cardoso et al., 2018; Farchi et al., 2017; Hoekstra et al., 2013b; Thomsen et al., 2018, 2019; Wikoff et al., 2018). This emerging discipline aims to balance the probability of an adverse health effect, in terms of incidence and severity, against the probability of beneficial effects attributable to an exposure to a specific dietary component (EFSA, 2010). So far, it has been mainly applied to the consumption of fish (ANSES, 2013; Becker et al., 2007; Domingo et al., 2007; EFSA, 2015; Hoekstra et al., 2013b; Ponce et al., 2000).

To evaluate the effect of food on human health, results from epidemiological cohort studies can be used. These studies aim to identify the risk factors associated with specific diseases (National Research Council, 2012) by following a group of populations over a limited time. A statistical treatment takes into account the confounding factors and calculates the excess risk attributable to a risk factor. The relation is primarily expressed in terms of relative risk (RR), defined by the

Abbreviations: CRC, colorectal cancer; CVD, cardiovascular disease; DALY, disability adjusted life years; RR, relative risk; GBD, Global Burden of Diseases; YLD, years of life lived with disability; YLL, years life lost

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https://doi.org/10.1016/j.fct.2019.05.023
Received 19 February 2019; Received in revised form 13 May 2019; Accepted 14 May 2019
Available online 16 May 2019

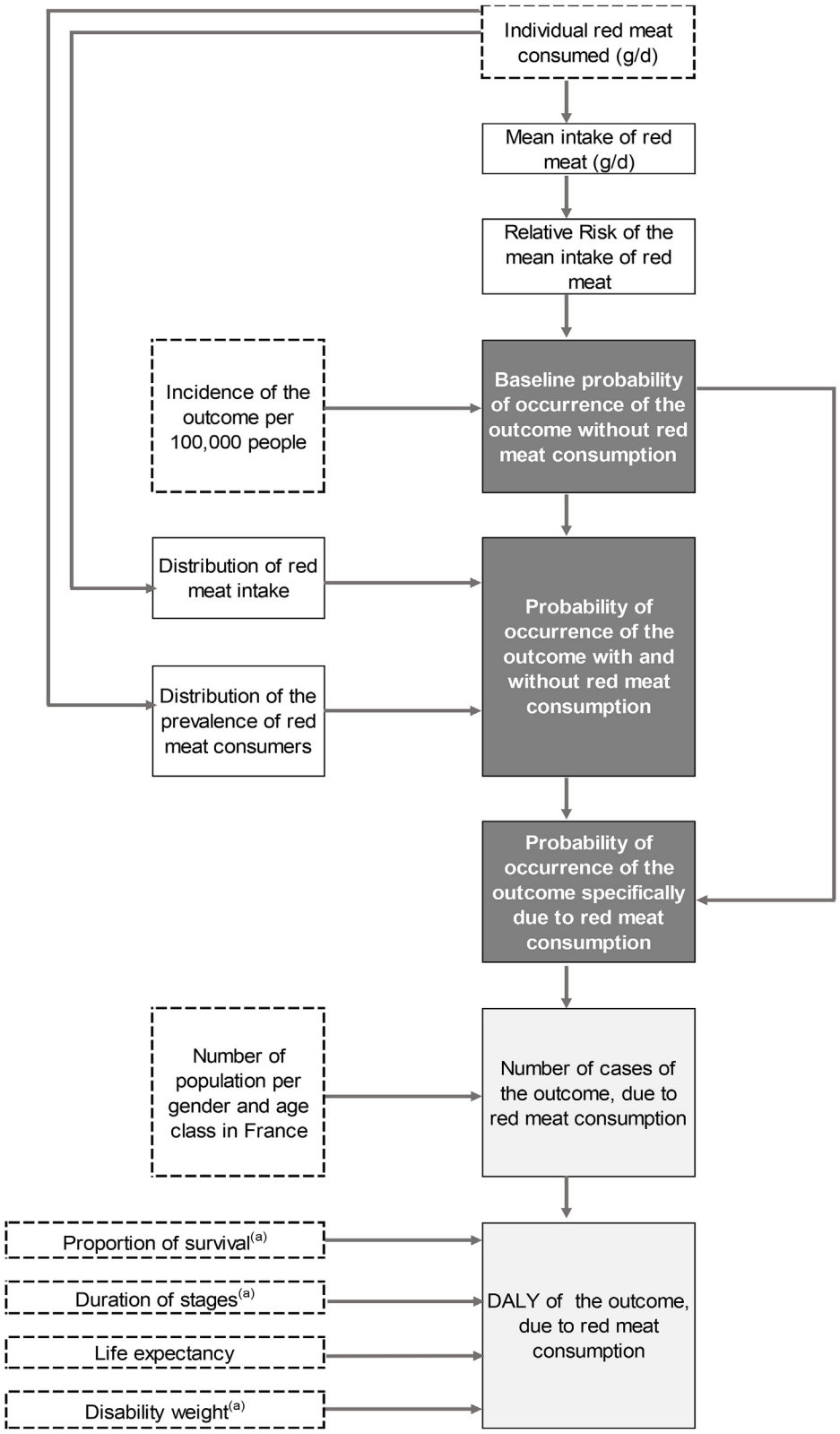

Fig. 1. Flowchart of the risk assessment model of colorectal cancer and cardiovascular disease in France per year, by age class and gender. White rectangles with dashed line correspond to the "Inputs", full line to "Intermediate calculation". Dark grey rectangles correspond to the "Intermediate output" and light grey rectangles correspond to the final output. (a) Only taken into account for colorectal cancer.

National Cancer Institute as "a measure of the risk of a certain event happening in one group compared to the risk of the same event happening in another group". Moreover, "a relative risk of greater than one or of less than one usually means that being exposed to a certain substance or factor either increases (relative risk greater than one) or decreases (relative risk less than one) the risk of cancer" (NCI, no date).

Risk assessment studies often limit themselves to the RR, but it is possible to go further, and estimate the number of cases and DALYs, as

done by the GBD study. Following the same strategy, in the present study, the burden of disease associated with red meat consumption by the French population was estimated in terms of DALYs. Indeed, in recent years, red meat has become a public health concern in France as well as in other western countries (Casalonga et al., 2017). In addition, red meat has been much consumed in France. In 2013, the average consumption of unprocessed red meat was 52.5 g per day per adult, compared to 34.9 g/day for unprocessed white meat (Duchène et al., 2017).

We decided to focus our study on colorectal cancer (CRC) and cardiovascular disease (CVD). This was done because, first, CRC is the cancer with the strongest evidence linking it to red meat (WCRF/AICR and project, 2017a). Second, CVD, because even if the strength of the evidence has not been clearly determined, it is the second most important cause of mortality in France, after tumors (INSEE, 2018). The World Cancer Research Fund International/Imperial College London and the World Health Organization have classified red meat consumption as "probably carcinogenic to humans". This classification was based on the positive association between the risk of CRC and the consumption of red meat, with a risk increase of 12% per increase of 100 g in red meat consumed (Bouvard et al., 2015; WCRF/AICR and project, 2017a), which led to the recommendation to limit red meat consumption to 500 g per week (ANSES, 2016). Likewise, an increase by 15% in the CVD mortality risk with an increase by 100 g in the amount of red meat consumed was found (Abete et al., 2014). The consumption of red meat might also be associated with breast cancer (Wolk, 2017), prostate cancer (WCRF/AICR, 2018; Wolk, 2017), nasopharyngeal cancer and lung cancer (WCRF/AICR, 2018). However, conclusions on the effect of consumption of unprocessed red meat by the WCRF remain limited, so we decided not to include them in this study. Therefore, a model quantifying both the risk and burden of disease of CRC and CVD due to red meat consumption in France was built.

Studies have already evaluated the impact of the consumption of red meat on CRC and/or CVD (Berjia et al., 2014; Farchi et al., 2017; Thomsen et al., 2018, 2019). However, the uncertainty and variability propagated by the model inputs is not often taken into account, and it is considered important to not ignore it (Nauta et al., 2018). Uncertainty corresponds to the lack of data and knowledge, and variability to the heterogeneity within a population (Cummins, 2017; Thompson, 2002; Vose, 2008). Separating the uncertainty and variability of the inputs enables identifying which of them are driving the output of the risk model and identifying what data will be needed to increase the precision and the confidence of the estimated output (Cummins, 2016). Despite the recommendations by international organizations (FAO/WHO, 2006), the separation of uncertainty and variability is not systematically done in risk assessment.

To summarize, the objective of this study was to estimate the burden of disease in France of CRC and CVD attributable to the consumption red meat. Based upon epidemiological studies, probabilistic models were set up for both gender and for specific age classes to quantify the risk of each outcome and the consequent burden of disease. A second order Monte Carlo simulation procedure was implemented to include uncertainty and variability, separately, in the analysis. Several consumption scenarios were analysed to help decision makers in refining their recommendations.

2. Model development

2.1. Model framework for colorectal cancer and cardiovascular risk assessment attributable to the consumption of red meat

The model was developed for males and females more than three years old. The age classes were 3–24, 25–44, 45–64, 65–84 and ≥ 85 years old. These age classes were defined in accordance with the age classes of the incidence data.

The flowchart of the risk assessment model is presented in Fig. 1. From red meat consumption in France, epidemiological studies, and French data on incidence of the outcome, the baseline probability of the outcome without red meat consumption was estimated. From this, the distribution of red meat intake in France, and the proportion of red meat consumers, the probability of the outcome with and without red meat consumption was calculated. Then the probability of the outcome specifically due to the consumption of red meat was estimated. Therefore, the number of cases and the corresponding burden of disease (DALY) per year, gender and age class were determined. Two outcomes were taken into account in the study: CRC occurrence and CVD mortality. The latter included diseases due to ischemic heart disease, acute coronary syndrome, myocardial infarction, cerebrovascular diseases, heart failure and venous thromboembolism. The relation between the consumption of red meat and the occurrence of disease, including both disease with full recovery and disease leading to fatalities, was established for CRC (WCRF/AICR and review, 2017b). However, in the case of CVD, this relation has been either found to be not significant (Kaluza et al., 2014, 2015; Micha et al., 2010), or, mortality and occurrence were mixed up in the estimation of RR (Bechthold et al., 2017; Kaluza et al., 2012; Micha et al., 2010; Yang et al., 2016).

Nevertheless, significant CVD mortality attributable to the consumption of red meat was established in Abete et al. (2014). For this reason, in the case of CVD, the model only estimated the number of deaths due to the consumption of red meat.

The inputs used in the model are summarized in Table 1 and Table 2.

2.2. Red meat consumption in France

Red meat consumption in metropolitan France was evaluated between 2005 and 2007 for males and females from 3 to 79 years old by the dietary survey INCA 2 (ANSES, 2014). A more recent dietary survey (INCA 3) was available (ANSES, 2017), but, unfortunately, the raw data were not accessible. Nevertheless, French food habits did not change over time regarding meat consumption. Indeed, for adults, for example, we observe only a slight decrease of the mean (49.7 g/d versus 47.3 g/d) (ANSES, 2014 and 2017). From the original data (ANSES, 2014), we exclusively selected the individuals who responded to the 7-day survey, which corresponds to 96% of the survey participants. Information about red meat consumption for individuals less than 3 years old and over 79 years old was not available. We then assumed that the consumption distribution of people in the age classes 65–84 and ≥ 85 years was the same as for people from 65 to 79 years old. The consumption of red meat took into account the consumption of unprocessed beef, pork, lamb and veal. More information about the individuals included in the study and the mean quantity of red meat consumed is available in Tables 1 and 2

From these consumption data, two variables were calculated: the mean consumption for each age class and gender and the probability density of consumption for red meat eaters. To estimate this latter, the function fitdist of the package fitdistrplus in the R software package (version 3.4.0) was used. Based upon the Akaike Information Criterion (AIC), the Gamma distribution provided the best fit, among the Weibull, Normal, Lognormal and Gamma distributions.

2.3. Health impact of the consumption of red meat

The health impact of the consumption of red meat is mostly evaluated by epidemiological studies with the effect then being expressed in terms of the RR. The inputs for both considered outcomes, i.e. CRC occurrence and CVD mortality, were determined from a meta-analysis. The values for an increase by 100 g in the consumption of red meat were 1.12 [95% CI: 1.00–1.25] (WCRF/AICR and project, 2017a) and 1.15 [95% CI: 1.05–1.26] (Abete et al., 2014), respectively. The epidemiological studies of the meta-analysis identified and took into

Table 1
Descriptions of and sources of information for inputs.

Input	Description		Notation for input	Obtained from
Current age	Mean age of the class		CA	–
French population data	Population in France		N	INSEE (2013)
	Life expectancy at the mean age of the class		LE	INSEE (2014)
Individuals of the study	Quantity of red meat consumed by red meat eaters		i	ANSES (2014)
	Proportion of red meat eaters		$Rconso$	ANSES (2014)
Colorectal cancer	Incidence of colorectal cancer		$Inc_{oc=CRC}$	Binder-Foucard et al. (2013)
	5-year net survival proportion after colorectal cancer		$Psurv$	Cowppli-Bony et al. (2016)
	Mean Relative Risk		$x_{oc=CRC}$	WCRF/AICR and project (2017a)
	Residual error of logarithm of RR		$\varepsilon_{oc=CRC}$	WCRF/AICR and project (2017a)
	Length of the outcome stage	diagnosis and treatment	DD_{DT}	Soerjomataram et al. (2012)
		remission	DD_R	Soerjomataram et al. (2012)
		latency before pre-terminal	DD_L	Soerjomataram et al. (2012)
		pre-terminal	DD_{PT}	Soerjomataram et al. (2012)
		terminal	DD_T	Soerjomataram et al. (2012)
	Disability weight of the stage	diagnosis and treatment	w_{DT}	GBD Cancer Collaboration (2017)
		remission	w_R	GBD Cancer Collaboration (2017)
		latency before pre-terminal	w_L	GBD Cancer Collaboration (2017)
		pre-terminal	w_{PT}	GBD Cancer Collaboration (2017)
		terminal	w_T	GBD Cancer Collaboration (2017)
	Proportion of permanent sequelae		$Pseq$	Soerjomataram et al. (2012)
	Disability weight of the sequelae		w_{seq}	GBD Cancer Collaboration (2017)
Cardiovascular disease	Incidence of cardiovascular disease		$Inc_{oc=CVD}$	DREES (2017)
	Mean Relative Risk		$x_{oc=CVD}$	Abete et al. (2014)
	Residual error of logarithm of RR		$\varepsilon_{oc=CVD}$	Abete et al. (2014)

account the major confounders for the Relative Risk, in order to only take into account the effect of consuming red meat on health, as much as possible. The main confounders were age, sex, smoking status, and body mass index, as well as the intake of fruits, vegetables, energy, and alcohol. To estimate RR, the World Cancer Research Fund International used a log-linear dose-response model (WCRF/AICR, 2017b) in which the confidence interval follows a normal distribution (Hamling et al., 2008; Woodward, 2014). This was used to determine the uncertainty around the RR parameters. We also hypothesized an effect of the consumption of red meat on CRC and CVD as soon as the individual consumed more than zero grams. Therefore, the dose-response per outcome was modelled by age class and gender considering the amount of red meat consumed in grams per day, as presented in Equation (1).

$$RR(\boldsymbol{i}_{(\boldsymbol{a},\boldsymbol{g})})_{oc} = e^{\left[\frac{\ln(x_{oc})}{100}\times i_{(a,g)}+\varepsilon_{oc}\right]} \quad (1)$$

Here, oc is the outcome concerned (CRC occurrence or CVD mortality), a is the age class, g is the gender, $i_{(a,g)}$ is the quantity of red meat consumed in grams per day, $RR(\boldsymbol{i}_{(\boldsymbol{a},\boldsymbol{g})})_{oc}$ the RR dose-response of the outcome, x_{oc} is the mean risk increase per 100 g increase in the consumption of red meat for outcome oc, a value provided by meta-analysis for the occurrence of CRC (WCRF/AICR and project, 2017a) and for CVD mortality (Abete et al., 2014) for CVD mortality, and ε_{oc} is the residual error of the logarithm RR for outcome oc.

Descriptions of and sources of information for the inputs are available in Tables 1 and 2.

2.4. Estimation of the probability of the occurrence of colorectal cancer and cardiovascular disease mortality attributable to the consumption of red meat

To estimate the probability of the outcome attributable to the consumption of red meat, the incidence rate of the outcome, defined as the number of new cases of the outcome during a year divided by the population size (CDC, no date), and RR were taken into account.

Combining these two inputs, the baseline probability of the outcome, which corresponds to the probability not associated to the consumption of red meat, was adapted from Hoekstra et al. (2013b), as follows:

$$P_{base\,(a,g)oc} = \frac{Inc_{(a,g)oc}}{RR(\bar{\boldsymbol{i}}_{(\boldsymbol{a},\boldsymbol{g})})_{oc} \times\ 100{,}000} \quad (2)$$

where $P_{base\,(a,g)oc}$ is the baseline probability of the outcome, $Inc_{(a,g)oc}$ is the incidence rate for the outcome for 100,000 people per years, $RR(\bar{\boldsymbol{i}}_{(\boldsymbol{a},\boldsymbol{g})})_{oc}$ is the RR of the mean consumption of red meat for the outcome, and $\bar{i}_{(a,g)}$ is the mean consumption of red meat.

The incidence rate of the occurrence of CRC was collected from a report of the French Institute for Public Health Surveillance, which estimated the number of cancer cases in France in 2012 per 100,000 person-years (Binder-Foucard et al., 2013). Incidence rate data corresponding to CVD mortality per 100,000 deaths per year were available in the 2017 report of the statistical data from the French Ministry of Solidarity and Health (DREES, 2017). We assumed that children under 3 years of age did not develop CRC or CVD. Incidence data are provided in Table 2.

The total probability of having the outcome, whether consuming red meat or not, was calculated assuming that people either ate or did not eat red meat, knowing the proportion of red meat consumers in the French population (Equations (3) and (4)):

$$P_{eff}(i)_{(a,g)oc} = P_{eff}(i>0)_{(a,g)oc} \times Prev_{eaters(a,g)} + P_{base\,(a,g)oc} \times (1 - Prev_{eaters(a,g)}) \quad (3)$$

$$P_{eff}(i>0)_{(a,g)oc} = RR(\boldsymbol{i}_{(\boldsymbol{a},\boldsymbol{g})})_{oc} \times P_{base\,(a,g)oc} \quad (4)$$

Where $P_{eff}(i)_{(a,g)oc}$ is the total probability of the outcome (with and without red meat consumption), taking into account the probability distribution of the quantity of red meat consumed (i). Here, $i_{(a,g)}$ is the quantity of red meat consumed by red meat eaters in grams per day, $P_{eff}(i>0)_{(a,g)oc}$ is the probability of the outcome when eating red meat ($i>0$), taking into account the probability distribution of the quantity of red meat consumed, $Prev_{eaters(a,g)}$ is the proportion of consumers of red meat in the French population estimated by a beta distribution using INCA 2 survey data, $P_{base\,(a,g)oc}$ is the baseline probability for the outcome (Equation (2)), and $RR(\boldsymbol{i}_{(\boldsymbol{a},\boldsymbol{g})})_{oc}$ is the RR of the quantity of red meat consumed.

The probability of the outcome (either CRC occurrence or CVD mortality) attributable to the consumption of red meat, $P_{rm(a,g)oc}(i)$, was then calculated by subtracting the baseline probability from the total probability:

Table 2
Implementation of the inputs either as deterministic values or as probability distributions.

Input	Notation for input	Gender	Model implementation per age class					Unit	Type
			3–24	25–44	45–64	65–84	> 85		
Current age	CA	Both	13.5	34.5	54.5	74.5	92.5	Years	D
French population data	N	Male	8,720,840	8,071,902	8,147,229	4,196,602	546,978	Number	D
		Female	8,389,958	8,203,441	8,559,150	5,286,389	1,251,801		
	LE	Male	78.73	79.48	81.43	86.48	95.87	Years	D
		Female	85.2	85.52	86.63	89.39	96.57		
Individuals of the study	i	Male	$\Gamma(2.21,\ 4.66 \times 10^{-2})^*$	$\Gamma(2.55,\ 3.87 \times 10^{-2})^*$	$\Gamma(2.47,\ 4.19 \times 10^{-2})^*$	$\Gamma(2.81,\ 5.61 \times 10^{-2})^*$	$\Gamma(2.81,\ 5.61 \times 10^{-2})^*$	g/day	U and V
		Female	$\Gamma(2.58,\ 6.94 \times 10^{-2})^*$	$\Gamma(2.71,\ 6.63 \times 10^{-2})^*$	$\Gamma(2.82,\ 6.63 \times 10^{-2})^*$	$\Gamma(2.59,\ 6.43 \times 10^{-2})^*$	$\Gamma(2.59,\ 6.43 \times 10^{-2})^*$		
	$Rconso$	Male	$B(695,61)^*$	$B(330,39)^*$	$B(404,27)^*$	$B(138,10)^*$	$B(138,10)^*$	Number	U
		Female	$B(772,107)^*$	$B(546,73)^*$	$B(477,61)^*$	$B(168,22)^*$	$B(168,22)^*$		
Colorectal cancer	$Inc_{oc=CRC}$	Male	0.27	5.63	80.27	318.26	436.96	Number per 100,000	D
		Female	0.42	6.09	53.85	180.69	295.94		
	$Psurv$	Male	$e^{\ln(0.71)+N(0,3.22\times10^{-2})^*}$	$e^{\ln(0.71)+N(0,3.22\times10^{-2})^*}$	$e^{\ln(0.69)+N(0,1.48\times10^{-2})^*}$	$e^{\ln(0.66)+N(0,1.17\times10^{-2})^*}$	$e^{\ln(0.5)+N(0,1.55\times10^{-2})^*}$	Percentage	U
		Female	$e^{\ln(0.72)+N(0,2.84\times10^{-2})^*}$	$e^{\ln(0.72)+N(0,2.84\times10^{-2})^*}$	$e^{\ln(0.72)+N(0,1.78\times10^{-2})^*}$	$e^{\ln(0.66)+N(0,1.15\times10^{-2})^*}$	$e^{\ln(0.51)+N(0,1.49\times10^{-2})^*}$		
	$x_{oc=CRC}$	Both	1.12					Number	D
	$\varepsilon_{oc=CRC}$	Both	$N(0,\ 5.69 \times 10^{-2})^*$					Number	U
	DD_{DT}	Both	1.08					Years	D
	DD_R	Both	3.92					Years	D
	DD_L	Both	1.267					Years	D
	DD_{PT}	Both	0.25					Years	D
	DD_T	Both	0.083					Years	D
	w_{DT}	Both	$N(0.288,\ 1.85 \times 10^{-1})^*$					Mean	U
	w_R	Both	$N(0.049,\ 2.15 \times 10^{-1})^*$					Mean	U
	w_L	Both	$N(0.049,\ 2.15 \times 10^{-1})^*$					Mean	U
	w_{PT}	Both	$N(0.451,\ 1.71 \times 10^{-1})^*$					Mean	U
	w_T	Both	$N(0.54,\ 1.53 \times 10^{-1})^*$					Mean	U
	$Pseq$	Both	0.13					Percentage	D
	w_{seq}	Both	$N(0.095,\ 1.87 \times 10^{-1})^*$					Mean	U
Cardiovascular disease	$Inc_{oc=CVD}$	Male	0.33	2.13	20.37	106.85	648.6	Number per 100,000	D
		Female	0.2	1.15	9.12	95.63	876.63		
	$x_{oc=CVD}$	Both	1.15					Number	D
	$\varepsilon_{oc=CVD}$	Both	$N(0,\ 4.65 \times 10^{-2})^*$					Number	U

U: uncertainty; V: variability; D: deterministic; * Following R parametrization.

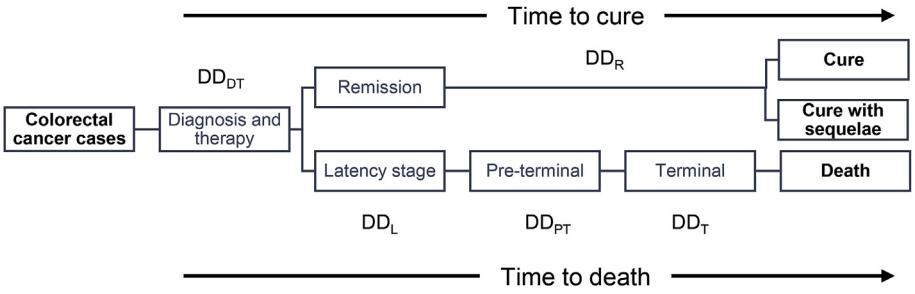

Fig. 2. Stages of progression of colorectal cancer, adapted from Soerjomataram et al. (2012) with duration of the stage: DD_{DT} as the duration for diagnosis and therapy, DD_R as the duration for remission before cure, DD_L as the duration for latency stage, DD_{PT} as the duration for pre-terminal stage and DD_T as the duration for terminal stage.

$$P_{rm}(i)_{(a,g)oc} = P_{eff\,(a,g)oc}(i) - P_{base\,(a,g)oc} \quad (5)$$

2.5. Estimation of the burden of disease in disability adjusted life years

The burden of disease of the outcome attributable to the consumption of red meat was estimated using the DALY indicator. This metric estimates the equivalent number of years in good health lost due to the outcome, and is commonly used in risk and benefit assessments (Hoekstra et al., 2012; Nauta et al., 2018; Tijhuis et al., 2012).

The estimation of DALY for CRC was adapted from previous studies (Soerjomataram et al., 2012). As represented in Fig. 2, the stages of the illness for people who survived were the diagnosis and therapy stages followed by the remission stage. For people who died, the stages were the diagnosis and therapy stages followed by the latency stage, pre-terminal stage and terminal stage. The calculation took into account the disability, from 0 (perfect health state) to 1 (death), and the duration of the sequelae for each stage of progression of the illness.

Finally, it was assumed that stoma was the only sequelae of colorectal cancer, and this sequelae was considered as permanent. The number of cases who survived (with or without sequelae) and the number of cases who died were calculated (Equations (6)–(9)).

$$N_{die.rm(a,g)} = (\overline{P_{rm}(i)_{(a,g)oc}} \times N_{(a,g)}) \times (1 - Psurv_{(a,g)}) \quad (6)$$

$$N_{sur.rm(a,g)} = (\overline{P_{rm}(i)_{(a,g)oc}} \times N_{(a,g)}) - N_{die.rm(a,g)} \quad (7)$$

$$N_{seq.rm(a,g)} = N_{sur.rm(a,g)} \times Pseq \quad (8)$$

$$N_{rec.rm(a,g)} = N_{sur.rm(a,g)} - N_{seq.rm(a,g)} \quad (9)$$

Here, $N_{die.rm(a,g)}$ is the number of people who died after a diagnosis of CRC attributable to red meat consumption, $N_{seq.rm(a,g)}$ is the number of people who survived with sequelae after a diagnosis of CRC attributable to red meat consumption, and $N_{rec.rm(a,g)}$ is the number of people who totally recovered after a diagnosis of CRC attributable to red meat consumption. In addition, $N_{(a,g)}$ is the number of individuals taken into account, in accordance with the French population statistics (INSEE, 2013), and $Psurv_{(a,g)}$ is the 5-year net survival rate after a diagnosis of CRC.

The duration of each stage and the proportion of stoma in the survivors were obtained from (Soerjomataram et al., 2012).

The CRC expressed in DALY was calculated as follows.

$$\begin{aligned} DALY_{rm(a,g)oc=CRC} = {} & N_{die.rm(a,g)} \times \left(\sum_s DD_{(s)} \times w_{(s)}\right) \\ & + N_{die.rm(a,g)} \times \left[LE_{(a)} - CA_{(a)} - \left(\sum_s DD_{(s)}\right)\right] \\ & + N_{seq.rm(a,g)} \times (LE_{(a)} - CA_{(a)} - DD_{DT}) \times w_{seq} \\ & + (N_{seq.rm(a,g)} + N_{rec.rm(a,g)}) \times \left(\sum_s DD_{(s)} \times w_{(s)}\right) \end{aligned} \quad (10)$$

Here, s indicates the stage of the illness, $DALY_{rm(a,g)oc=CRC}$ the disability adjusted life years of CRC due to red meat consumption, $DD_{(s)}$ the duration of stage s, $w_{(s)}$ the disability weight at stage s as taken from GBD Cancer Collaboration (2017), $CA_{(a)}$ the current age at diagnosis of colorectal cancer, $LE_{(a)}$ the life expectancy at age a, and w_{seq} the disability weight of sequelae.

For each age class, the mean age was calculated considering the current age at the moment of diagnosis of CRC. Life expectancy was estimated from mortality tables (INSEE, 2014), taking into account the mean age of the age class.

The estimation of the DALY for CVD ($DALY_{rm(a,g)oc=CVD}$) only took into account mortality, i.e. YLL, calculated from epidemiological data:

$$DALY_{rm(a,g)oc=CVD} = N_{rm(a,g)oc=CVD} \times (LE_{(a)} - CA_{(a)}) \quad (11)$$

The output was considered significant when the lower bound of the 95% confidence interval was higher than zero.

3. Model implementation

3.1. Identification of sources of uncertainty and variability and implementation

To estimate the outputs, the model needs to be given inputs. Inputs are variables defined by either one value or a range of different values with their probability of occurrence reflecting the variability and/or the uncertainty associated with the data (Boué et al., 2015; Membré and Boué, 2017).

Four types of inputs were defined:

- *Deterministic input* is a fixed number for a given age class and gender. Life expectancy at the mean age of the class, current age at diagnosis, incidence of the outcome, length of outcome stage and the proportion of permanent sequelae are deterministic inputs in the model.
- Data with *uncertainty exclusively,* such as the proportion of red meat eaters estimated through a beta probability distribution, or the 5-year net survival rate after CRC built with a normal distribution on the natural logarithm of the data (Cowppli-Bony et al., 2016).
- Input with *variability and uncertainty separated* and quantifiable. For red meat consumption, the variability comes from the different levels of consumption of red meat for the different individuals in a given age class and gender. Uncertainty is due to the gap between the real and the estimated quantity of red meat consumed, obtained with a gamma distribution. The separation of uncertainty and variability was carried out using the function mcdata in the package mc2d of R (version 3.4.0).
- Input with *variability and uncertainty not separated*. The RR error term, ε_{oc}, of the outcome represents the uncertainty due to the compilation of the meta-analyses and implementation of the model (choice between linear or non-linear dose-response) (Hamling et al., 2008; Woodward, 2014) but also the variability due to biological differences between individuals. A discrimination between these is not feasible, as RR is not a datum but the result of meta-analyses. Disability weights are uncertain due to the adjustments of data but also variable due to biological differences, the stage of the outcome

and the age and gender of the individuals. For this kind of input, we chose to quantify the variability and the uncertainty as only uncertainty.

The type of implementation of each input is given in Table 2.

3.2. Monte Carlo 2D simulation

Inputs were implemented using probability distributions and simulated with Monte Carlo simulation in two dimensions (MC2D). In our models, 10,000 iterations were run to capture the uncertainty and 10,000 iterations for the variability, using the mcstoc function in R (mc2d package). To verify the stability of the outputs, three simulations were carried out for each age class and gender. Variations less than 5% were achieved.

3.3. Sensitivity analysis

First of all, a sensitivity analysis was performed to identify the major sources of uncertainty in the output. The current distribution of red meat intake in France for males in the age class 65–84 was used as the benchmark for the comparison (no uncertainty, only variability). For CVD, the simulation was run, sequentially with uncertainty due to the fitted distribution of red meat consumption, uncertainty from the proportion of eaters of red meat, and uncertainty due to RR. In addition to the previously mentioned uncertainties, for CRC, the influence of the uncertainty from the 5-year net survival rate and uncertainty due to the disability weight was evaluated. Each confidence interval of the DALY from the simulations was compared with the confidence interval of the simulation taking into account all uncertainties of the model.

Then, the influence of the consumption of red meat, corresponding to the main source of variability in the model, was tested by running various scenarios of red meat consumption. We established consumption scenarios for both genders for the 45–64 and 65-–84 age classes. There were considered 100,000 people in each gender and age class to evaluate the effect of a specific quantity of red meat consumed, independently of the original number of people in this gender and age class. The following levels of consumption of red meat were tested: 25 g/d, 50 g/d, 75 g/d, 100 g/d and 125 g/d.

3.4. Non-quantifiable sources of uncertainty

When building the model, several assumptions were made; they were considered as extra sources of uncertainty. Although non-quantifiable, their influence on the output was qualitatively appraised. We adopted the same method as suggested in “BRAFO tiered approach for benefit–risk assessment of foods” (Hoekstra et al., 2012). The effect of each hypothesis on the output of the model was estimated, using information from the literature, as follows: *no change or little effect* on the output, *likely overestimation*, *likely underestimation*, *overestimation with certainty*, *underestimation with certainty,* or, *no possible conclusion*.

4. Results

4.1. Burden of disease associated with consumption of red meat

The mean probability of CRC cases and CVD deaths associated with the consumption of red meat are represented with 95% confidence intervals by age class and gender in Fig. 3. For both outcomes, males were more at risk than females, and the risk increased with age. The risk rose drastically beyond the 45–64 age class for both genders for CRC occurrence, with a risk 13 times and 9 times higher than the previous age class for males and females, respectively. For CVD, the risk increased beyond the 65–84 age class for females, with a risk over 9 times higher than for the 45-–64 age class. Before this age, the risk was close to zero. Furthermore, for both outcomes, the more advanced the age was, the higher the gap between the probabilities of the outcome for males and females.

Males ≥85 years old were the most likely to be affected, for both outcomes. Moreover, the mortality from both outcomes seemed to be similar for the same age class and gender, except for those over 85 years old (Fig. 4).

For males, being 45–64 and being 65-–84 were the major contributors to the burden of disease (expressed in DALY, Fig. 5) due to CRC attributable to the consumption of red meat, with 5 [95% CI = 0.4–14] and 5 [95% CI = 0.2–13] DALY per 100,000 people per year, respectively. The same holds for females, with 3 [95% CI = 0–9] and 3 [95% CI = 0–10] DALY per 100,000 people per year, respectively.

The two major contributor population groups for this CVD were the male population in the 45–64 and 64–85 age classes with 5 [95% CI = 1–11] and 5 [95% CI = 1–12] DALY per 100,000 people per year, respectively.

4.2. Analysis of different scenarios of red meat consumption and effect on burden of disease

In the developed model, the different levels of red meat consumption were the only sources of variability. To estimate the effect of red meat intake on the output, independently of the number of people in the age class, a consumption scenario for 100,000 people for males and females 45–64 and 65–84 years old was run. The results are presented in Table 3.

When the quantity of red meat consumed increases, the number of DALYs increases proportionally, since a linear RR dose-response was used in the model. For both age classes and outcomes, males were more at risk, whatever the quantity consumed. However, for CRC occurrence, the number of DALY was significantly higher than zero only for a consumption equal to or higher than 100 g/day, for both genders for both age classes. In contrast, for cardiovascular death, the number of DALY was significant for red meat intake equal to or higher than 75 g/day, for both genders and age classes.

4.3. Influence of uncertainty and assumptions on model outputs

A sensitivity analysis enabled identifying the main source of uncertainty from the inputs taken into account for the calculation of the DALYs. Of all the variables taken into account in the model, RR was the largest source of uncertainty (Fig. 6).

Indeed, the uncertainty interval for RR was more than 40 times larger than that for disability-weight in the CRC estimation of DALY, and 25 times larger than that for the proportion of eaters of red meat in the CVD estimation. The uncertainty from levels of consumption, proportion of eaters of red meat, and 5-year net survival rate did not really affect the results for colorectal cancer as much as the uncertainty only due to consumption when estimating the burden of disease for CVD mortality.

Beside this quantitative uncertainty analysis, a qualitative analysis of the influence of the assumptions made to build the model on the outputs is provided in Table 4. The hypotheses “stoma was the only sequelae taken into account in the quantification of the disability of colorectal cancer” and “Red meat consumption only enhanced mortality due to cardiovascular disease” underestimated with certainty the estimated output. The assumption that “the sequelae after colorectal cancer was permanent” overestimated the output with certainty. Other assumptions had little effect on the output.

5. Discussion

The probabilistic risk assessment model built in this study enabled estimating the risk, the number of deaths, and DALYs for both CRC and CVD attributable to the consumption of red meat.

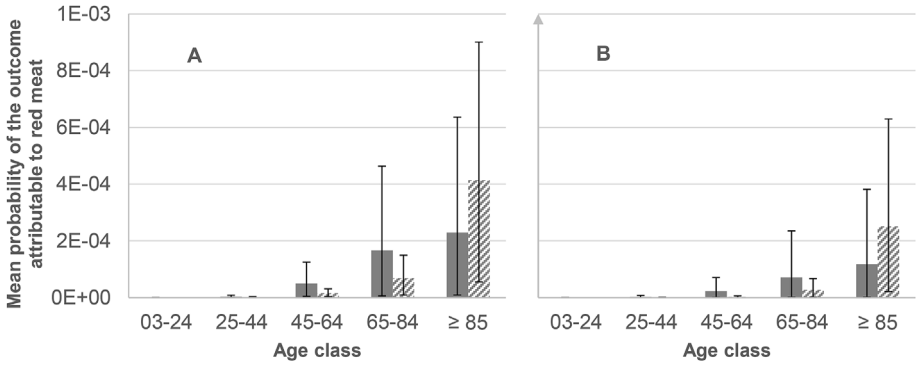

Fig. 3. Mean probability of cases of colorectal cancer (filled bars) and deaths from cardiovascular diseases (dashed bars) due to the consumption of red meat for males (A) and females (B). Full lines represent the 95% uncertainty intervals around mean values.

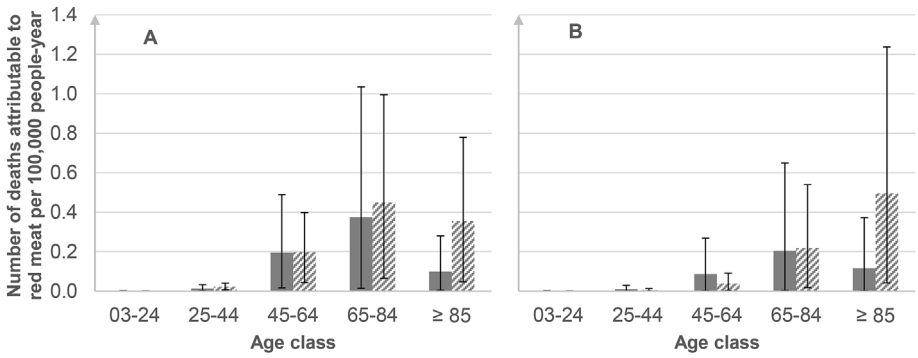

Fig. 4. Estimated number of deaths from colorectal cancer (filled bars) and cardiovascular diseases (dashed bars) attributable to the consumption of red meat per 100,000 people per year for males (A) and females (B). Full lines represent the 95% uncertainty.

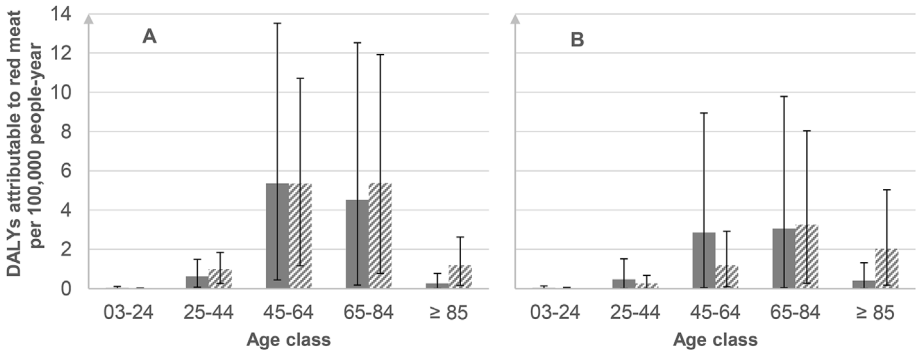

Fig. 5. Estimated number of DALYs from colorectal cancer (filled bars) and cardiovascular diseases (dashed bars) attributable to the consumption of red meat per 100,000 people per year for males (A) and females (B). Full lines represents the 95% uncertainty.

Males were more at risk than women for both outcomes, especially those older than 45 (Fig. 3), as also found in a study carried out in Alberta, Canada (Grundy et al., 2016). This difference is partially explained by the lower consumption of red meat by women, with a mean intake of 35 g/day compared with 50 g/day for men. Heme iron is suspected to be the main component in the mechanism leading to the outcome (Wolk, 2017) and in the developed countries, red meat is the richest source of this nutrient (Czerwonka and Tokarz, 2017). This nutrient and its mechanism of carcinogenicity has been associated with CRC (Bastide et al., 2011; Pierre et al., 2004) and CVD (Ascherio et al., 1994; Qi et al., 2007; Sullivan, 1981). Organic components from cooking, such N-nitroso-compounds, polycyclic aromatic compounds, and heterocyclic aromatic amines, have also been suspected of carcinogenicity (Bouvard et al., 2015; Cross et al., 2010; Sinha and Rothman, 1999). Recent studies have evaluated the role of several chemical components in the carcinogenicity of the consumption of red meat, concluding that their roles were not well defined (Domingo and Nadal, 2016, 2017), and that the consumption of meat was not the main factor responsible for the dietary exposure to these components (Domingo, 2017). The difference between genders might also be explained by the compositions of the diets of women and men. According to the dietary survey INCA 2, women consumed more fresh dairy products, fish and fruit than men, who, in contrast, consumed a higher proportion of meat, cured meat, potatoes and dried fruit (AFSSA, 2009; ANSES, 2016). Studies of the carcinogenic mechanism of CRC have shown that the consumption of the dietary calcium salts from dairy products and chlorophyll from vegetables reduces heme iron trapping (Balder et al., 2006; Bastide et al., 2016; Pierre et al., 2003), and consequently its harmful effect. In addition, polyphenols, such as those contained in fruits and red wine, decrease the oxidative effect of heme iron, by inhibiting lipid peroxidation and DNA damage (Bastide et al., 2011, 2016; Lampe, 1999). In Denmark, replacing 14 g of red meat by 25 g of fish would lead to an average decrease of 13 DALY per 100,000 adults (Thomsen et al., 2018). Furthermore, in World Cancer Research

Table 3
Number of DALYs calculated for colorectal cancer and cardiovascular disease for each scenario of consumption for males and females 45–64 years old and 65–84 years old. Calculated for 100,000 people per year in combinations of age, gender and intake. The value is represented with its 95% confidence interval.

Outcome	Age class	Gender	Intake (g/d)				
			25	50	75	100	125
Colorectal cancer occurrence	45–64	Male	18 [0–87]	37 [0–105]	57 [0–125]	77 [1–147]	98 [23–167]
		Female	14 [0–65]	28 [0–79]	42 [0–94]	57 [1–108]	73 [17–125]
	65–84	Male	36 [0–167]	72 [0–203]	111 [0–242]	150 [4–281]	189 [40–319]
		Female	26 [0–119]	52 [0–147]	79 [0–173]	107 [2–201]	135 [31–229]
Cardiovascular disease mortality	45–64	Male	18 [0–62]	37 [0–81]	56 [8–100]	76 [28–121]	97 [48–141]
		Female	6 [0–20]	12 [0–26]	18 [3–33]	25 [9–39]	32 [16–46]
	65–84	Male	42 [0–147]	87 [0–191]	133 [18–236]	180 [65–285]	229 [114–333]
		Female	27 [0–94]	56 [0–121]	84 [12–151]	115 [41–181]	146 [72–213]

Fund International conclusions, the consumption of milk and calcium probably reduce the risk of CRC, whereas processed meat and alcoholic drinks increases this risk (WCRF/AICR, 2017b).

The estimated number of deaths was 3.1 [95% CI = 1.9–4.5] per 100,000 people per year (Fig. 4) with 3.4 [95% CI = 1.5–6.0] cases per 100,000 people per year for CRC. These latter correspond to 1950 [95% CI = 1200–2800] and 2170 [95% CI = 950–3830] respectively for the French population per year. The major contributor was being a male in

Table 4
Assumptions made in the model development and their influence on the output.

Hypothesis	Justification of the hypothesis	Influence on the output[a]
French food habits did not change over this period of time	Data for colorectal cancer incidence and population were from 2012 and data from incidence of cardiovascular deaths were from 2013 to 2014, but consumption data dated from 2005 to 2007.	=
The number and life expectancy of individuals in France in 2012 were the same as in 2013 and 2014	Most of the time, the data in the model were from 2012. However, the data available for cardiovascular disease mortality were from 2013 to 2014.	+/-
Children under 3 years of age did not suffer from colorectal cancer or cardiovascular disease death	The first class of incidence for colorectal cancer included an age group ranging from 0 to 14 years. For cardiovascular disease mortality, the first class evaluated included all cases under 25 years old. The consumption for children under 3 years of age was not available. It was then assumed that all the people suffering from colorectal cancer and cardiovascular disease were more than 3 years old. However the occurrence of the outcomes has not been clearly demonstrated.	+/-[b]
The consumption habits of seniors over 80 years were identical to those for individuals 65–79 years old	The consumption for people over 80 years old was not available. The hypothesis was based on the fact that consumption did not vary much for adults over 45 years old and elderly people.	+/-
The consumption of red meat had a linear effect, as suggested in meta-analysis studies	In some studies, the dose-responses of the consumption of red meat and of the consumption of processed meat were not linear (Bechthold et al., 2017; Chan et al., 2011; WCRF/AICR and review, 2017b).	+/-
The effect of consuming red meat was effective from a consumption greater than zero grams	It was assumed that even a small quantity of red meat could increase the risk. However, in some studies, the risk of colorectal cancer was considered as increasing only from 70 g/d of consumed red meat (Alexander et al., 2015; Aykan, 2015).	+
The time of each stage of the colorectal processes was a deterministic value	Although there was an effect of age, gender and the stage of diagnosis on the duration of each stage of the colorectal processes, the literature only gave deterministic values, in general expressed by the mean value (Soerjomataram et al., 2012).	=
Life expectancy was the same for all individuals with the same gender in the same age class	The mortality tables did not give the uncertainty of the life expectancy. The data were expressed in deterministic form for the mean age of the class.	=
Proportion of sequelae due to colorectal cancer was a fixed value	In the absence of information, the proportion of sequelae after colorectal cancer was hence in deterministic form.	=
Stoma was the only sequelae taken into account in the quantification of the disability of colorectal cancer	Stoma was the sequelae for which reliable data were the most available in the literature. However colorectal cancer may have other sequelae, such as incontinence, bowel function problems, urination problems, gastrointestinal problems and sexual problems (Gatta et al., 2007).	- -
The sequelae after colorectal cancer was permanent	The duration of life with sequelae was not available in the literature.	+ +
Red meat consumption only enhanced mortality due to cardiovascular disease	Although epidemiological studies did not find a significant quantitative link between the consumption of red meat and the occurrence of cardiovascular disease, a period of disease may occur before death.	- -
Relative risk, disability weight and length of the stages of illness were identical for females and males for all age classes	Data was given with no distinction by gender or age class.	+/-

[a] (=) no change/little effect, (+) likely overestimation, (−) likely underestimation, (+ +) overestimation with certainty, (- -) underestimation with certainty, (±) no possible conclusion.
[b] Effect for age class 3–24 years old.

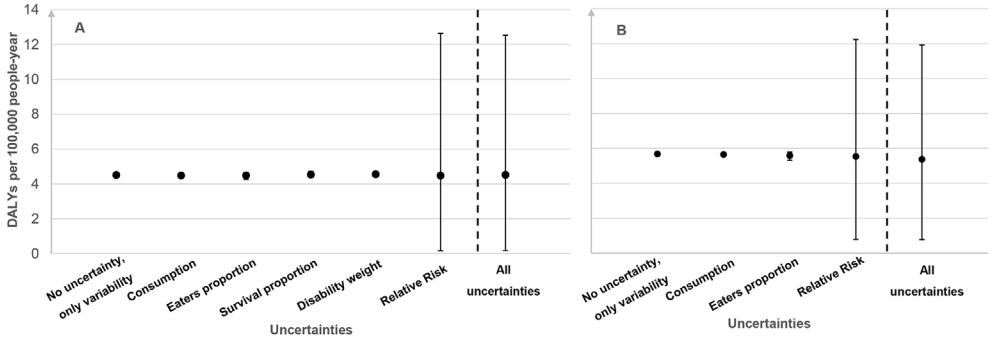

Fig. 6. Influence of uncertainty on DALYs for males aged 65–84 due to colorectal cancer (A) and cardiovascular disease (B) for 100,000 people-year. Full line represents the 95% uncertainty interval around the mean represented by the full circle.

the 65–84 age class.

The attributable fraction, calculated as the ratio between the number of cases due to the consumption of red meat ($N_{rm(a,g)oc}$) and the total incidence of the outcome (Inc_{oc}) in France estimates that for the French population, 5% of CRC cases were attributable to the consumption of red meat. To have an order of magnitude and to check the realism of the results, these estimates were compared with those for other countries whose dietary habits are not too far from French food habits. Our results were in line with recent estimates from the International Agency for Research on Cancer (IARC, 2018). This proportion was also similar to those calculated for the United States, the United Kingdom (WCRF/AICR, no date), and New Zealand (Richardson et al., 2016) with 5% of the population attributable fraction, as well as those for Northern and Central Europe (7.8% of CRC in men, and 5.8% in women) (Norat et al., 2002). This value is also close to that of a study of the Italian population which concluded that if people changed their beef consumption habits to an intake of 150 g/week, 3.7% of the deaths due to CRC would be avoided (Farchi et al., 2017). In contrast, in Australia the attributable risk of CRC in 2010 was estimated to be higher (18%), but there was no distinction between processed meat and red meat (Nagle et al., 2015).

In our study, CVD deaths in France attributable to the consumption of red meat were estimated as 1%. An Italian study also quantified the effect of the consumption of beef on CVD mortality. They estimated 3.3% of the deaths from CVD would be avoided if people ate only 150 g/week of beef (Farchi et al., 2017). In Brazil, a study of the attributable fraction to consuming red meat concluded there was a negligible effect in comparison to the attributable fraction due to consuming processed meat (7.7%) (Rezende et al., 2016). This could be explained by the mean consumption of the Brazilian population, which was found to be under 70 g/d.

Our study went further than the attributable fraction since it estimated the burden of disease of both CRC occurrence and CVD mortality attributable to consuming red meat, by expressing them in DALYs. This composite metric is the most used one in risk and benefit assessments (Hoekstra et al., 2012; Nauta et al., 2018). It has the advantage of making a comparison between different health effects, taking into account morbidity and mortality (Murray, 1994; Pires et al., 2019), whereas a comparison based upon the number of cases or fatalities would have been incomplete. In this study, if the estimation had stopped with the number of deaths, it would have been concluded that males from 65 to 84 years old were the population most affected by both outcomes. However, when taking into account morbidity in addition, as done by using DALY, we can observe that males from 45 to 64 years old were the most affected by the outcome. Indeed, if the outcome induces a fatality, this population group will lose a higher number of years lived compared to their expected life expectancy. In addition, cases which survive but with sequelae, will live longer with a disability caused by the outcome, compared with the population group 65–84 years old (Figs. 4 and 5). Therefore, for decision making, such as making further recommendations, DALY is more relevant.

Another advantage of using DALY to express the risk is its unit: reporting results in years is easier for the public to understand than a dimensionless output such as RR or population attributable fraction. DALYs are expressed in the same unit as life expectancy, which is widely known by the public and used in the mass media.

This study estimated 19 [95% CI = 8–33] DALYs per 100,000 people per year for CRC attributable to the consumption of red meat, corresponding to 12,170 [95% CI = 5,260–21,170] DALY per year for the French population. Similar estimates were obtained by the Institute for Health Metrics and Evaluation for CRC, which calculated 17 DALY per 100,000 people per year of the attributable part of a diet high in red meat in France (IHME, 2018). Another study found 17 DALY per 100,000 people per year in Denmark (calculated from 394 DALY per 100,000 people per year when consuming or not red meat minus 377 DALY per 100,000 people per year without red meat intake) (Berjia et al., 2014). A Norway study cited by Thomsen et al., in 2018 estimated approximately 40 DALY per 100,000 people attributable to the consumption of red meat (Thomsen et al., 2018).

The CVD DALY for the French population attributable to the consumption of red meat was estimated to be 21 [95% CI = 12–32] DALY per 100,000 people per year corresponding to 12,960 [95% CI = 7,330–19,360] DALY per year. This is 1% of the total DALY estimated by the Institute for Health Metrics and Evaluation for the French population (IHME, 2018).

Our study highlighted a higher effect of the consumption of red meat on CVD mortality than on CRC, for the oldest age class, both in terms of number of deaths and DALYs (Figs. 4 and 5). This is so even if the number of YLD was excluded from the CVD. This exclusion was done because the relation between the consumption of red meat and the occurrence of CVD, including both full recovery and occurrence of the disease leading to fatalities, was either found to be not significant (Kaluza et al., 2014, 2015; Micha et al., 2010), or mortality and occurrence were mixed up in the estimation of RR (Bechthold et al., 2017; Kaluza et al., 2012; Micha et al., 2010; Yang et al., 2016). Consequently, without scientific quantitative evidence, only DALY for cardiovascular death were estimated. This could be then considered as higher than the estimate in the present paper. Based on the GBD-compare-tool (IHME, 2018), which determines the number of DALY by risk, year, country, gender and age class, we could address the number of burden of disease attributable to CVD associated with the consumption of red meat under the assumption that red meat consumption induced disease before death. In the estimates of the GBD study, the YLD made up 21% and 27% of the total DALY, for males and females, respectively, whatever the source of illness. Based on this information, it was then possible to recalculate the number of DALY due to CVD including both morbidity and mortality: the median estimate of the mean was 17 DALY per 100,000 people per year for French males and 10 per 100,000 people per year for French females associated with the consumption of red meat. Unfortunately, to our best knowledge, there

is no existing quantification of the DALY attributable to the consumption of red meat on CVD in the literature, to compare with our results.

The burden of CRC and CVD attributable to the consumption of red meat can be compared with other burdens of illness and risk factors in France. For French males, it was shown that the consumption of red meat induced 11 DALY per 100,000 people per year for CRC and 13 DALY per 100,000 people per year for CVD. These values are comparable to the burden caused by sexually transmitted infections excluding HIV/AIDS (11 DALY per 100,000 French males) but they are lower than those observed for liver cancer due to alcohol (160 DALY per 100,000 French males) (IHME, 2018). In addition, we can compare the DALYs attributable to CRC and CVD due to the consumption of red meat (4% and 1% respectively) with other risk factors. For example, the GBD-compare-tool estimated a higher risk factor contribution of tobacco (CRC: 8.5%; CVD: 18%) and alcohol (CRC: 28.19%; CVD: 12.3%) for both diseases (IHME, 2018).

The use of the DALY metric also enabled making consumption scenarios. It confirmed that the recommendation to consume less than 500 g per week of red meat, issued by the authorities (ANSES, 2016; HCSP, 2017), would be enough to prevent the risk of CRC attributable to red meat consumption. This estimate is also in line with the study of Norat et al. (2002), in which a decrease of CRC risk was estimated (7%–24%) in case the intake was lowered to 70 g/week of red meat (Norat et al., 2002). However, to prevent CVD attributable to the consumption of red meat, the consumption by the oldest individuals should be under 65 g per day.

In this study, quantifiable and unquantifiable uncertainties were taken into account, and their effects on the model outputs were assessed (Table 4 and Fig. 6), as recommended by international organizations (FAO/WHO, 1999).

The quantification of the uncertainty took into account the fitted distribution of red meat intake, the proportion of red meat consumers, RR and the disability weight. However, the study also highlighted some difficulties in tackling uncertainty and variability. For instance, RR, identified as a source of uncertainty in our model due to model parameter estimation (Frey, 1997; Krewski et al., 1999) within a random effect model meta-analysis (Vieira et al., 2017), included also individual susceptibility variability. Indeed, a family history of colorectal cancer, the presence of adenomatous polyps, previous colorectal cancers, and infectious diseases such as Crohn's disease and ulcerative colitis, increase the risk of CRC (Haggar and Boushey, 2009). In addition, diabetes, high cholesterol and high blood pressure are not always taken into account in the statistical estimation, and induce a variability in the RR of the CVD estimation (Abete et al., 2014; O'Donnell and Elosua, 2008). Nevertheless, the estimation of RR is generally implemented in risk–benefit models as a source of uncertainty (Thomsen et al., 2018).

Disability weights also combined variability and uncertainty. Some authors classify it as only variability (Havelaar et al., 2004), the confidence interval representing the variability of the severity of the disability, but others implement it as an uncertainty (Boué et al., 2017; Thomsen et al., 2018).

Another source of uncertainty comes from the hypotheses made when building the study.

Indeed, the duration of each stage of colorectal cancer, the proportion of cases with sequelae, and the life expectancy, were implemented as deterministic values. The effect of these data on the output could not be assessed since they were considered as fixed. The hypothesis that the CRC had a dose-response without any threshold, i.e., effective starting from any consumption greater than zero grams (implicit when assuming a log-linearity of the dose-response), was considered as leading to an overestimation of the outcome. Furthermore, for both outcomes, recent studies have also shown that the dose-response is non-linear, which might underestimate or overestimate the outcome for lower consumption. The same conclusion was drawn about the hypothesis that the life expectancy of the French population was constant over time. Due to the lack of data, no conclusion was possible about the influence of some of the assumptions, such as: children under three years old did not suffer from either outcome, the consumption habits of individuals over 80 years old were identical to those of individuals from 65 to 79 years old, and, RR and disability weight were assumed to be the same for both genders and age classes. The CVD burden of disease may be underestimated because the consumption of red meat was only associated with mortality due to CVD. The CRC burden of disease was also underestimated because stoma was considered as the only sequelae taken into account in the quantification of the disability of colorectal cancer. We assumed no change in the outputs stemming from a change in food habits, because the level of consumption of red meat did not vary much from 2005 to 2013. However, the estimation provides a snapshot of the effect of the consumption of red meat without considering any previous change in it in the population over the years. On the other hand, the CRC burden of disease was overestimated because the sequelae were considered as effective until the end of the life of a CRC survivor. In addition, the effect of exposure is not visible immediately, which induces an additional uncertainty (Nauta et al., 2018). Some studies have assumed a period of 8 years of latency between the exposure and the outcome for CRC (Grundy et al., 2016) and 10 years for CVD (Milner et al., 2015), while in our study, the latency was taken to be 6–7 years.

Nonetheless, despite the inherent uncertainty due to the biological data and particularly the epidemiological data, the results obtained in this study can be interpreted as showing that some differences in the burden of disease were observed, such as between the highest and lowest intakes, as well as between the youngest and oldest populations.

In further studies, this burden will be balanced by the microbiological risks and nutritional benefits of red meat in a broader risk–benefit assessment. Indeed, red meat is also a source of microbiological foodborne illnesses. In 2017, it was estimated that pig and beef meat were responsible for 6.2% of the total outbreaks of such illnesses (ECDC/EFSA, 2018). On the other hand, red meat has beneficial aspects, due to its nutrients, especially iron, which is one of the major nutritional deficiency in the world (Kassebaum and GBD 2013 Anemia Collaborators, 2016).

In conclusion, the effects of the consumption of red meat on the risk of CRC and CVD have been estimated and expressed in DALYs. The study estimated 19 [95% CI = 8–33] DALY per 100,000 people per year for CRC and 21 [95% CI = 12–32] DALY per 100,000 people per year for CVD, associated with the consumption of red meat. As done previously (Cardoso et al., 2018; Hoekstra et al., 2013a, 2013b; Thomsen et al., 2018, 2019; Verhagen et al., 2012; Wikoff et al., 2018), the present work will be included in a more comprehensive risk and benefit assessment.

Acknowledgement

The Region Pays de la Loire and INRA are acknowledge for founding the PhD project associated with this study

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