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Interactions between meat intake and genetic variation in relation to colorectal cancer

Vibeke Andersen · Ulla Vogel

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Abstract Meat intake is associated with the risk of colorectal cancer. The objective of this systematic review was to evaluate interactions between meat intake and genetic variation in order to identify biological pathways involved in meat carcinogenesis. We performed a literature search of PubMed and Embase using “interaction”, “meat”, “polymorphisms”, and “colorectal cancer”, and data on meat–gene interactions were extracted. The studies were divided according to whether information on meat intake was collected prospectively or retrospectively. In prospective studies, interactions between meat intake and polymorphisms in *PTGS2* (encoding COX-2), *ABCB1*, *IL10*, *NFKB1*, *MSH3*, *XPC* ($P_{\text{int}} = 0.006, 0.01, 0.04, 0.03, 0.002, 0.01$, respectively), but not *IL1B*, *HMOX1*, *ABCC2*, *ABCG2*, *NR1I2* (encoding PXR), *NR1H2* (encoding LXR), *NAT1*, *NAT2*, *MSH6*, or *MLH1* in relation to CRC were found. Interaction between a polymorphism in *XPC* and

meat was found in one prospective and one case–control study; however, the directions of the risk estimates were opposite. Thus, none of the findings were replicated. The results from this systematic review suggest that genetic variation in the inflammatory response and DNA repair pathway is involved in meat-related colorectal carcinogenesis, whereas no support for the involvement of heme and iron from meat or cooking mutagens was found. Further studies assessing interactions between meat intake and genetic variation in relation to CRC in large well-characterised prospective cohorts with relevant meat exposure are warranted.

Keywords Colorectal carcinogenesis · Genetic susceptibility · Genetic epidemiology · Polymorphisms · Gene–environment interactions · Diet–gene interactions · Lifestyle

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Introduction

Colorectal cancer (CRC) is a major health problem worldwide. In the Western World, CRC is the third most common cancer and the one with the second highest mortality (WCRF 2014). In the developing countries, the incidence is increasing due to demographic changes and due to implementation of Western lifestyle. Lifestyle factors, including diet, are considered to be the main causes of CRC (WCRF 2014). High intake of red and processed meat, animal fat, alcohol, and smoking is the factor that has been associated with the risk of CRC, whereas high intake of dietary fibres, fruit and vegetables, and physical activity is considered to protect from CRC (Huxley et al. 2009; WCRF 2014). The World Cancer Research Fund has evaluated observational and experimental evidence linking

the intake of red and processed meat to CRC as convincing (WCRF 2014). Furthermore, they judged that half of all CRC cases may be prevented by relevant lifestyle changes (WCRF 2014). Accordingly, advancing the understanding of underlying mechanisms for developing CRC may have large implications for human health by forming the basis for preventive interventions.

Various mechanisms by which intake of red and processed meat may promote colorectal carcinogenesis have been suggested (Santarelli et al. 2008; Ferguson 2010; Alexander and Cushing 2011; Alexander et al. 2011; Chan et al. 2011; Erridge 2011; Zur 2012). Meat is a source of fat, protein, dietary iron, zinc, sulphur, and vitamins and may contain microbes developed during storage, various additives, cooking mutagens, and antibiotics. These meat compounds may be carcinogenic by various mechanisms as illustrated in Fig. 1. For example, heterocyclic amines (HAC), polycyclic aromatic hydrocarbons (PAH), and *N*-nitroso compounds (NOC) present in meat or arising during processing and cooking at high temperature may introduce DNA damage leading to the generation of mutations and cancer (Santarelli et al. 2008). The carcinogenic effects will depend on the efficiency of the human metabolism of the compound (activation, degradation, or excretion) and on the efficiency of repair of the DNA damage (Fig. 1). Hence, HCAs may be activated by *N*-acetyltransferases (encoded by *NAT1* and *NAT2*) to form carcinogens acting in the colon epithelium, whereas phase II xenobiotic metabolising enzymes such as UDP-glucuronosyltransferases (encoded by the UGTs) may detoxify the cooking carcinogens (Gilsing et al. 2012; Ollberding et al. 2012). Also, protein fermentation by the colonic bacteria may lead to the formation of carcinogenic substances such as hydrogen sulphide (H_2S) (Hamer et al. 2012; Windey et al. 2012; Andersen 2014a). In particular, meat contains high amounts of fat and proteins, including organic sulphur-containing proteins, which may contribute to enhance the microbial production of H_2S . This leads to DNA damage, up-regulation of pro-inflammatory COX-2, and suppression of anti-inflammatory butyrate. Thus, a diet high in animal fat was found to increase the amount and activity of the *Bilophila Wadsworthia* in an animal model (Devkota et al. 2012). Because this bacterium reduces sulphite (SO_3^{2-}) from diet to H_2S by anaerobic oxidation and because meat is a particularly rich source of organic sulphur, this results in high colonic production of H_2S (Carbonero et al. 2012). Besides inducing DNA damage, H_2S and its ion sulphide (S^{2-}) has been associated with the up-regulation of COX-2; impaired oxidation of butyrate, which is the most important fuel in the intestinal cells (Windey et al. 2012); and induction of intestinal hyperproliferation (Carbonero et al. 2012). Thus, meat intake, intestinal microbes, and individual factors may interact and affect intestinal

inflammation (Jia et al. 2012). Furthermore, a diet high in fat may increase the risk of CRC by hormonal mechanisms (Fig. 1). Moreover, n-6 polyunsaturated fatty acids (n-6 PUFAs) from meat are converted into arachidonic acid that is further metabolised by the cytochrome P450 oxygenase (CYP), the cyclooxygenase (COX), and the lipoxygenase (LOX) pathways to pro- and anti-inflammatory prostaglandins (PG) and leukotrienes (LT) including PGE_2 and LTB_4 , which have been found to be involved in colorectal carcinogenesis (Wang and DuBois 2010a, b; 2013). Also, indications that microbial factors present in meat or arising during storage may be involved in CRC have been found in (Erridge 2011; Zur 2012). Thus, intake of meat may potentially affect intestinal homeostasis by a range of various mechanisms leading to somatic mutations, epigenetic changes, and impaired balance between proliferation and apoptosis resulting in cancer development as summarised in Fig. 1.

Genetically determined variations in the activity of enzymes or pathways may modify the processes mentioned in Fig. 1 and thereby influence meat-related risk of CRC. Hence, assessment of gene–environment interactions provides a tool to identify the combinations of genes and environmental factors involved in CRC because the presence of an interaction indicates that the two factors are involved in the same process (Vogel et al. 2007; Andersen et al. 2009, 2010, 2012a, b, 2013a, b). Furthermore, use of functional polymorphisms, i.e. polymorphisms which lead to changed protein activity, may help the biological understanding. Gene–environment interaction studies may generate knowledge on biological mechanisms and may provide indications for primary prevention. In gene–environment interaction studies, human metabolism and the complexity of lifestyle factors are taken into account. This is difficult to achieve by other means. We therefore reviewed the literature on interactions between meat intake and polymorphisms in relation to CRC in order to identify pathways involved in the effects of meat intake.

Methods

A systematic review was carried out according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al. 2009) (Fig. 2). PubMed and Embase were searched for various combinations of “meat”, “colorectal cancer”, “snp(s)”, “gene variant”, and “polymorphisms” [e.g. (“red and processed meat” OR “red meat” OR “processed meat” OR “meat”) AND “colorectal cancer” AND (“genetic” OR “polymorphism” OR “polymorphisms” OR “gene variants” OR “snps” OR “snp”)] with no restrictions (e.g. on years considered) resulting in 239

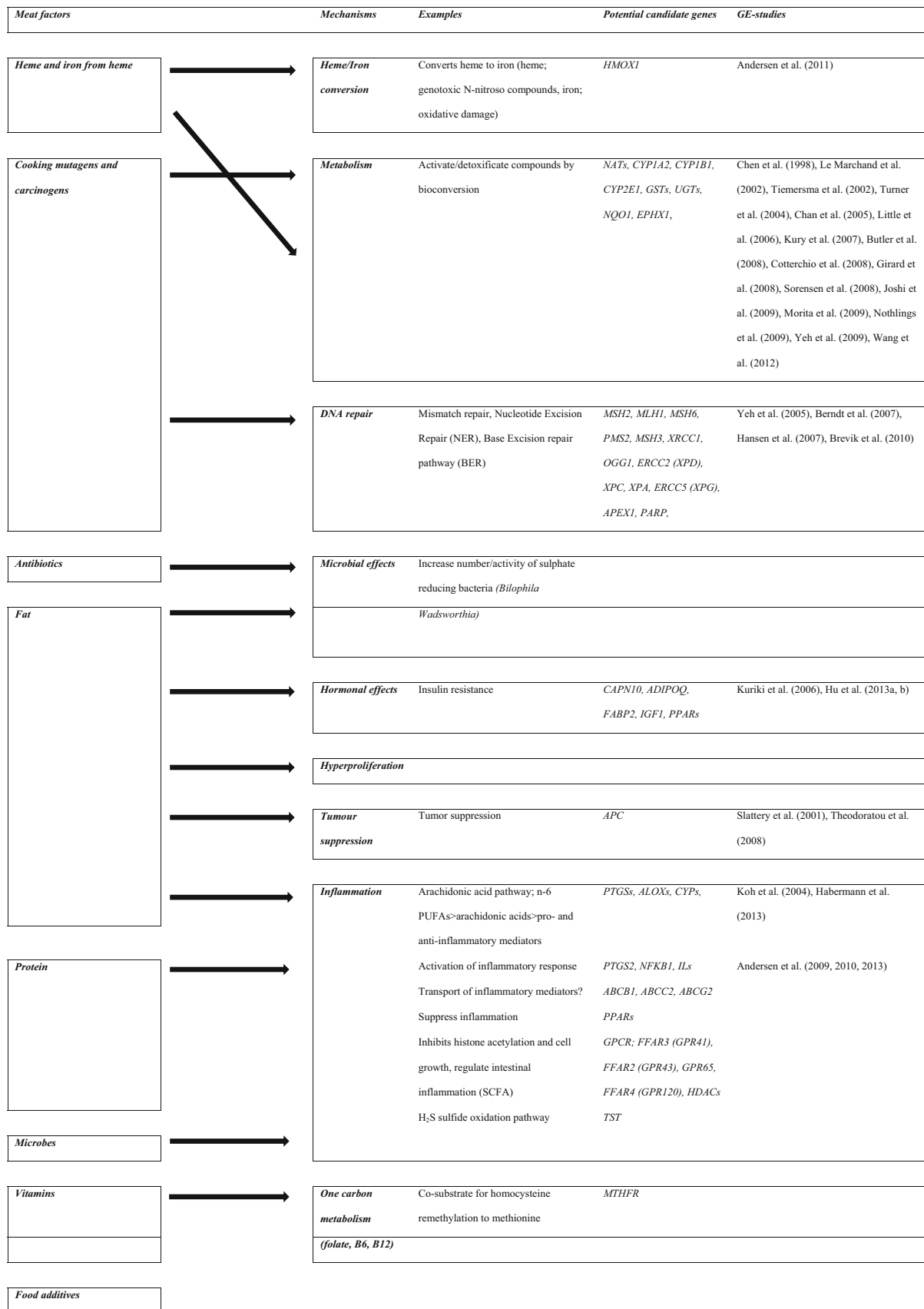
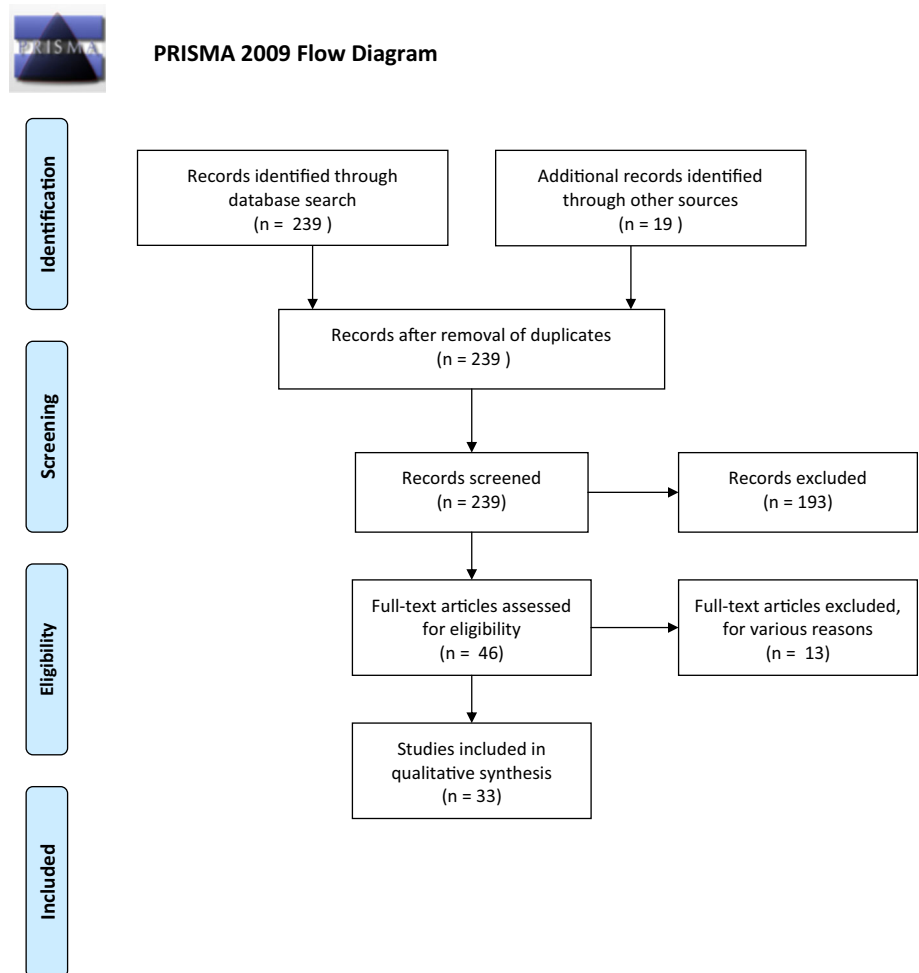


Fig. 1 Examples of potential mechanisms by which meat may affect colorectal carcinogenesis

Fig. 2 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of the retrieved studies



abstracts *in total* (January, May, and August 2014). Articles from abstracts suggesting that they presented original data on polymorphisms and meat interaction were retrieved and read. All studies which reported original data on meat intake and gene interactions and which were published in English were included.

Studies were excluded due to missing data on the interaction analyses between meat intake and gene variants in relation to CRC, interaction with meat-related variables (proxies), and not meat itself was performed and with less than 25 cases in the subgroup analyses.

Information on study design, the number of participants, incidence rate ratios (IRR) and odds ratios (OR), P value for interaction (P_{int}) from the interaction analyses between meat intake and polymorphisms in relation to CRC was retrieved from the studies when present. When rs number was not provided by the authors, the rs number was retrieved using PubMed Gene (<http://www.ncbi.nlm.nih.gov/gene/324>) by selecting SNP gene view and provided when the rs number could be unambiguously identified. Furthermore, polymorphisms which deviated

from Hardy–Weinberg equilibrium were excluded (one polymorphism).

P_{int} indicates whether there was statistically significant interaction between the effects of meat intake and genotypes in relation to the risk of CRC.

The retrieved studies were divided according to the time when the information on meat intake was sampled into prospective studies (data collected before the diagnosis of CRC, Table 1) and case–control studies (data collected after the diagnosis of CRC, Table S1). P values adjusted for confounders and not corrected for multiple testing were chosen whenever possible (Table 1, Table S1). P value below 0.05 was considered statistically significant.

Replication of found results in an independent cohort is an important tool to identify gene–environment interactions in genetic epidemiology (Andersen and Vogel 2014a, b). In the present work, identification of gene–environment interactions was performed in the prospective studies (discovery cohorts). We regarded the finding as replicated if the results were reproduced in another prospective study or in a case–control study.

Table 1 Interactions between meat intake and polymorphisms in relation to the risk of colorectal cancer in prospective cohorts

Gene	rs-number ^d	N_{cases}	$N_{sub-cohort}$	IRR/OR (95 % CI) ^a	P_{int}^b	Comments ^c	First author	Year	References
<i>Cooking carcinogens and mutagens</i>									
<i>NAT1</i>		120	123			4	Chen	1998	Chen et al. (1998)
	NAT*10 allele	92	98		0.19	4			Chen et al. (1998)
<i>NAT2</i>		131	125			4			Chen et al. (1998)
		81	96		0.56	4			Chen et al. (1998)
<i>NAT2</i>		107	267			5	Chan	2005	Chan et al. (2005)
		76	476		0.07	5			Chan et al. (2005)
<i>NAT1</i>				0.99 (0.94–1.04)		2, 3, 6	Sorensen	2008	Sorensen et al. (2008)
				0.98 (0.90–1.05)	>0.40	2, 3, 6			Sorensen et al. (2008)
<i>NAT2</i>				1.00 (0.95–1.06)		2, 3, 6			Sorensen et al. (2008)
				0.96 (0.90–1.03)	>0.40	2, 3, 6			Sorensen et al. (2008)
<i>NAT1</i>		362	527			7	Nothlings	2009	Nothlings et al. (2009)
	No*10	482	818		0.77	7			Nothlings et al. (2009)
<i>NAT2</i>		750	1149			7			Nothlings et al. (2009)
	Slow/med	242	344		0.44	7			Nothlings et al. (2009)
<i>NAT1</i>		362	527			8			Nothlings et al. (2009)
	No*10	482	818		0.93	8			Nothlings et al. (2009)
<i>NAT2</i>		750	1,149			8			Nothlings et al. (2009)
	Slow/med	242	344		0.13	8			Nothlings et al. (2009)
<i>AHR</i>	rs2066853	364	394		0.07	12	Gilsing	2012	Gilsing et al. (2012)
<i>UGT1A</i>	rs6714486	364	394		0.06	12			Gilsing et al. (2012)
	rs17868299	364	394		0.05	12			Gilsing et al. (2012)
<i>UGT1A</i>	rs2011404	364	394		0.08	12			Gilsing et al. (2012)
<i>CYP2E1</i>	rs915908	364	394		0.05	12			Gilsing et al. (2012)
<i>UGT1A</i>	rs6717546	364	394		0.04	12			Gilsing et al. (2012)
<i>UGT1A</i>	rs12466997	364	394		0.08	12			Gilsing et al. (2012)
<i>Arachidonic acid pathway</i>									
<i>PTGS2 (COX-2)</i>	rs689566	900	1,686	1.02 (0.98–1.05)		1, 2, 3	Andersen	2013	Andersen et al. (2013b)
	A-1195G	47	61	1.06 (0.87–1.29)	0.54	1, 2, 3			Andersen et al. (2013b)
	rs20417	701	1,256	0.99 (0.95–1.03)		1, 2, 3			Andersen et al. (2013b)
	G-765C	235	478	1.08 (1.01–1.15)	0.006	1, 2, 3			Andersen et al. (2013b)
	rs5275	430	720	1.04 (0.99–1.09)		1, 2, 3			Andersen et al. (2013b)
	T8473C	501	1,018	1.01 (0.96–1.05)	0.29	1, 2, 3			Andersen et al. (2013b)
	TC-CC								
<i>Transport proteins</i>									

Table 1 continued

Gene	rs-number ^d		N_{cases}	$N_{\text{sub-cohort}}$	IRR/OR (95 % CI) ^a	P_{int}^b	Comments ^c	First author	Year	References
<i>ABCB1 (MDR1)</i>	rs1045642	3435	73	118	1.08 (1.00–1.16)		1, 2, 3	Andersen	2009	Andersen et al. (2009)
			286	647	1.00 (0.95–1.06)	0.02	1, 2, 3			Andersen et al. (2009)
	rs3789243	Intron 3	81	224	0.95 (0.89–1.02)		1, 2, 3			Andersen et al. (2009)
<i>ABCG2 (BCRP)</i>	rs2231142	C421A	278	541	1.03 (0.98–1.09)	0.01	1, 2, 3			Andersen et al. (2009)
	rs717620	C-24T	296	592	1.02 (0.97–1.08)		1, 2, 3			Andersen et al. (2009)
<i>ABCC2 (MRP2)</i>			63	173	0.99 (0.91–1.08)	0.40	1, 2, 3			Andersen et al. (2009)
	rs2273697	G1249A	260	508	1.02 (0.97–1.07)		1, 2, 3	Andersen	2012	Andersen et al. (2012b)
	rs3740066	C3972T	129	280	1.03 (0.95–1.12)	0.72	1, 2, 3			Andersen et al. (2012b)
<i>Cytokines</i>			238	480	1.05 (0.99–1.11)		1, 2, 3			Andersen et al. (2012b)
	rs1800872	C-592A	151	308	0.98 (0.91–1.05)	0.10	1, 2, 3			Andersen et al. (2012b)
	rs3024505		143	301	1.01 (0.96–1.08)		1, 2, 3			Andersen et al. (2012b)
<i>IL10</i>			246	487	1.03 (0.97–1.10)	0.69	1, 2, 3			Andersen et al. (2012b)
	rs1800872	C-592A	238	470	1.02 (0.97–1.07)		1, 2, 3, 9	Andersen	2012	Andersen et al. (2012b)
	rs3024505		140	305	1.02 (0.95–1.11)	0.92	1, 2, 3, 9			Andersen et al. (2012b)
<i>IL1B</i>			268	553	1.02 (0.96–1.08)		1, 2, 3, 9			Andersen et al. (2012b)
	rs4848306	C-3737T	110	222	1.03 (0.96–1.10)	0.78	1, 2, 3, 9			Andersen et al. (2012b)
	rs1143623	G-1464C	596	1072	1.02 (0.98–1.06)		1, 2, 3	Andersen	2013	Andersen et al. (2013b)
<i>Transcription factors</i>			353	676	1.00 (0.95–1.06)	0.46	1, 2, 3			Andersen et al. (2013b)
	rs28362491	-94 ins/del	648	1,200	1.00 (0.96–1.04)		1, 2, 3			Andersen et al. (2013b)
	rs1523127	A-24381C	297	565	1.06 (1.00–1.11)	0.04	1, 2, 3			Andersen et al. (2013b)
<i>NFKB1</i>			336	560	1.01 (0.96–1.07)		1, 2, 3			Andersen et al. (2013b)
	rs2276707	C8055T	605	1,186	1.02 (0.98–1.06)	0.65	1, 2, 3			Andersen et al. (2013b)
	rs6785049	A7635G	454	925	1.02 (0.97–1.06)		1, 2, 3			Andersen et al. (2013b)
<i>NR1I2 (PXR)</i>			492	824	1.02 (0.97–1.07)	0.94	1, 2, 3			Andersen et al. (2013b)
	rs28362491	-94 ins/del	389	773	1.00 (0.96–1.05)		1, 2, 3			Andersen et al. (2013b)
	rs1523127	A-24381C	557	983	1.03 (0.98–1.07)	0.40	1, 2, 3			Andersen et al. (2013b)
<i>Transcription factors</i>			122	307	0.96 (0.90–1.04)		1, 2, 3	Andersen	2010	Andersen et al. (2010)
	rs2276707	C8055T	261	456	1.03 (0.97–1.08)	0.03	1, 2, 3			Andersen et al. (2010)
	rs6785049	A7635G	131	261	1.04 (0.97–1.12)		1, 2, 3			Andersen et al. (2010)
<i>NFKB1</i>			252	502	1.01 (0.95–1.06)	0.20	1, 2, 3			Andersen et al. (2010)
	rs2276707	C8055T	237	448	1.02 (0.96–1.08)		1, 2, 3			Andersen et al. (2010)
	rs6785049	A7635G	146	315	1.01 (0.95–1.08)	0.74	1, 2, 3			Andersen et al. (2010)
<i>NR1I2 (PXR)</i>			137	264	1.01 (0.95–1.07)		1, 2, 3			Andersen et al. (2010)

Table 1 continued

Gene	rs-number ^d	N_{cases}	$N_{\text{sub-cohort}}$	IRR/OR (95 % CI) ^a	P_{int}^b	Comments ^c	First author	Year	References
<i>NR1H2 (LXR)</i>	rs1405655	246	499	1.02 (0.96–1.08)	0.60	1, 2, 3			Andersen et al. (2010)
		40	76	1.01 (0.93–1.10)		1, 2, 3			Andersen et al. (2010)
	rs2695121	343	687	1.02 (0.96–1.07)	0.94	1, 2, 3			Andersen et al. (2010)
		117	227	1.03 (0.96–1.11)		1, 2, 3			Andersen et al. (2010)
<i>Heme oxygenase HMOX1 (HO-1)</i>	rs2071746	266	536	1.01 (0.96–1.07)	0.43	1, 2, 3			Andersen et al. (2010)
		118	260	1.00 (0.93–1.08)		1, 2, 3	Andersen	2011	Andersen et al. (2011a, b)
	265	503	1.02 (0.97–1.08)	0.55	1, 2, 3			Andersen et al. (2011a, b)	
<i>DNA repair MSH3</i>	rs184967	127				8, 10	Berndt	2007	Berndt et al. (2007)
		65			0.08	8, 10			Berndt et al. (2007)
<i>MSH3</i>	rs26279	85				8, 10			Berndt et al. (2007)
		102			0.002	8, 10			Berndt et al. (2007)
<i>MSH6</i>	rs1042821	118				8, 10			Berndt et al. (2007)
		54			0.29	8, 10			Berndt et al. (2007)
<i>MLH1</i>	rs1799977	84				8, 10			Berndt et al. (2007)
		101			0.40	8, 10			Berndt et al. (2007)
<i>XPC</i>	Rs2228001 ^d	141	307	1.17 (0.71–1.92)		7, 11	Hansen	2007	Hansen et al. (2007)
		204	392	1.11 (0.70–1.75)		7, 11			Hansen et al. (2007)
		50	98	3.70 (1.70–8.04)	0.01	7, 11			Hansen et al. (2007)
<i>XPA</i>	A23G	176	339	1.30 (0.78–2.17)		7, 11			Hansen et al. (2007)
		187	359	1.41 (0.87–2.26)		7, 11			Hansen et al. (2007)
		31	90	0.76 (0.34–1.66)	0.37	7, 11			Hansen et al. (2007)
<i>ERCC2 (XPD)</i>	Rs1799793 ^d	159	333	1.25 (0.69–2.26)		7, 11			Hansen et al. (2007)
		191	354	1.25 (0.83–1.87)		7, 11			Hansen et al. (2007)
		46	108	1.22 (0.61–2.45)	1.00	7, 11			Hansen et al. (2007)
<i>XPC</i>	Rs2228001 ^d	141	307	0.63 (0.23–1.69)		8, 11			Hansen et al. (2007)
		204	392	0.94 (0.41–2.15)		8, 11			Hansen et al. (2007)
		50	98	3.78 (0.64–22.29)	0.20	8, 11			Hansen et al. (2007)
<i>XPA</i>	A23G	176	339	0.58 (0.23–1.48)		8, 11			Hansen et al. (2007)
		187	359	1.87 (0.73–4.83)		8, 11			Hansen et al. (2007)
		31	90	0.31 (0.06–1.64)	0.06	8, 11			Hansen et al. (2007)

Table 1 continued

Gene	rs-number ^d	N_{cases}	$N_{\text{sub-cohort}}$	IRR/OR (95 % CI) ^a	P_{int}^b	Comments ^c	First author	Year	References
<i>ERCC2 (XPD)</i>	Rsl799793 ^d	159	333	1.07 (0.38–3.03)	8, 11				Hansen et al. (2007)
		191	354	0.75 (0.33–1.68)	8, 11				Hansen et al. (2007)
		46	108	1.93 (0.43–8.63)	0.49	8, 11			Hansen et al. (2007)

^a Odds ratio (OR) or incidence rate ratio (IRR)

^b P for interaction (P_{int}) between meat and the genotypes in relation to CRC has been retrieved from the studies and may have been calculated in different ways

^c Comments: (1) Incidence rate ratio (IRR) for colorectal cancer per intake of 25 g red or processed meat. (2) Adjusted for sex and age, smoking status, alcohol, HRT status (women only), BMI, NSAID use, and dietary fibre. (3) P value for interaction between the genotype and dietary intake for the fully adjusted risk estimate. (4) Tertile analyses of daily red meat intake (≤ 0.5 , >0.5 –1, >1). (5) Tertile analyses of intake of beef, pork, or lamb as a main dish (≤ 0.5 , >0.5 servings per day). (6) IRR for colorectal cancer per intake of 25 g red meat. (7) Intake of red meat. (8) Intake of processed meat. (9) These data (Andersen et al. 2012a, b) are also included in (Andersen et al. 2013a, b). (10) Adjusted for age, race, and energy intake. (11) Adjusted for average smoking intensity, intake of alcohol, fruits/vegetable, fish/poultry, red meat, dietary fibres, BMI, and hormone replacement therapy. (12) Interactions between intake of benzo[a]pyrene (B[a]P), 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx), 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline (DiMeIQx), and combined nitrate and nitrite, respectively, and the polymorphisms

^d rs number was not provided by the authors. Rs number has been identified and provided as described in the “Methods” section in cases where the rs number could be unambiguously identified

Data from (Chen et al. 1998; Tiemersma et al. 2002; Sorensen et al. 2008; Chan et al. 2011) have been presented in a previous review (Andersen et al. 2013a, b).

Results

Table 1 and Table S1 show results on interactions between meat intake and polymorphisms in relation to CRC from prospective and case–control studies, respectively.

Cooking carcinogens and mutagens

Prospective studies have evaluated the interaction between fast and slow acetylators and meat intake in relation to the risk of CRC (Table 1) (Chen et al. 1998; Chan et al. 2005; Sorensen et al. 2008; Nothlings et al. 2009; Gilsing et al. 2012). Whereas one small study found interaction between the number of servings per day and *NAT2* acetylator status (Chan et al. 2005), no association was found between the amount of total or processed meat intake or number of servings and *NAT1* or *NAT2* status in relation to the risk of CRC in three other studies (Chen et al. 1998; Sorensen et al. 2008; Nothlings et al. 2009).

Arachidonic acid pathway

Interaction between meat intake and the *PTGS2* G-765C (rs20417) polymorphisms was found in a prospective study ($P_{\text{int}} = 0.006$) (Table 1) (Andersen et al. 2013a, b). Thus, individuals carrying the G-765C C-variant allele were at 8 % increased risk of CRC per 25 g red and processed meat per day in contrast to the homozygous wild-type carriers whose risk of CRC was unaffected by meat intake.

Transport proteins

Interactions between meat intake and polymorphisms in *ABCB1* in relation to the risk of CRC were found in a prospective cohort, whereas no interactions were found for the two other transport proteins, *ABCC2* and *ABCG2* (Table 1) (Andersen et al. 2009, 2012a, b). Intake of meat was associated with increased risk among the *ABCB1* C3435T homozygous wild-type and intron 3 G-rs3789243-A-variant allele carriers, whereas the risk of CRC for carriers of the other alleles was unaffected by meat intake (Andersen et al. 2009).

Cytokines

Interaction between meat intake and the marker polymorphism near *IL10* rs3024505 was found in a prospective cohort, whereas no interaction was found with the

functional *IL10* C-592A nor with three functional *IL1B* polymorphisms (Andersen et al. 2013a, b) (Table 1).

Transcription factors

No interactions were found between meat intake and the genes *NR1I2* and *NR1H2* encoding PXR and LXR in relation to CRC (Table 1) (Andersen et al. 2010). Interactions were found between meat intake and *NFKB1* (encoding the anti-inflammatory subunit p50/p105 of NFκB) -94 ins/del (rs2836249) in relation to the risk of CRC in a prospective cohort (Table 1) (Andersen et al. 2010). Carriers of the *NFKB1* -94ins/del del-variant alleles were at 3 % higher risk of CRC per 25 g meat eaten per day compared to homozygous wild-type allele carriers who had no risk by meat intake (Table 1).

Heme oxygenase

No interactions were found between the functional *HMOX1* A-413T (rs2071746) polymorphism and meat intake in relation to CRC (Table 1) (Andersen et al. 2011a).

DNA repair

A statistically significant interaction between the intake of processed meat and the mismatch repair gene *MSH3* T1036A (rs26279) and a suggestive interaction with R940Q (rs184967) was found in a prospective case-only study of approximately 185 persons ($P_{\text{int}} = 0.002$ and 0.08, respectively) (Table 1) (Berndt et al. 2007). Interpretation of the results was not possible because possible functional effects of the polymorphisms were not known (Berndt et al. 2007).

A statistically significant interaction between the intake of red meat and *XPC* Lys939Gln and a suggestive interaction between the intake of processed meat and *XPA* A23G was found in a prospective study ($P_{\text{int}} = 0.01$ and 0.06, respectively) (Hansen et al. 2007) (Table 1). Homozygous variant carriers of *XPC* Lys939Gln were at high risk of CRC by the intake of red meat compared to the homozygous wild-type carriers (reference) [IRR = 3.78 (1.70–8.04) and 1.17 (0.71–1.92) per 100 g of red meat per day, respectively, $P_{\text{int}} = 0.01$] (Hansen et al. 2007). The *XPC* Lys939Gln polymorphism was also identified in a case–control study (Steck et al. 2014) (Table S1). They found that homozygous wild-type carriers had an increased risk by high meat compared to low meat intake in the same group, whereas variant allele carriers had no increased risk by high meat intake [OR = 1.5 (1.0–2.2) and 1.0 (0.9–1.8) for homozygous wild-type carriers with high meat and low meat intake, respectively, $P_{\text{int}} = 0.05$] (Steck et al. 2014) (Table S1). Thus, in contrast to the study above, increased

risk for high well-done red meat intake was found among homozygous wild-type carriers in the case–control study.

Discussion

In this review, we evaluated gene–environment interactions between meat intake and genetic variation in relation to CRC in order to identify the biological pathways underlying meat-related CRC carcinogenesis (Fig. 1; Table 1, and S1). The retrieved studies were divided into prospective studies (Table 1) and case–control studies (Table S1) according to the risk of recall bias. We assessed whether found results were replicated in an independent cohort as this is considered an important tool to identify gene–environment interactions in genetic epidemiology.

The meat content of HCAs, PAHs, and NOCs has been suggested to confer the risk of CRC in humans (Santarelli et al. 2008; Ferguson 2010; Alexander and Cushing 2011; Alexander et al. 2011; Erridge 2011; Zur 2012). Prolonged high-temperature cooking of meat leads to the production of HCAs and PAHs, especially grilling, barbecuing, and frying (Ferguson 2010). In this review, we reported that one small study found interaction between the number of servings per day and *NAT2* acetylator status (Chan et al. 2005), whereas no association was found between the amount of total or processed meat intake or number of servings and *NAT1* or *NAT2* status in relation to the risk of CRC in three other studies (Chen et al. 1998; Sorensen et al. 2008; Nothlings et al. 2009). The results of this review are thus in accordance with a large prospective study of 1757 CRC cases found no association between the intake of HCA from meat and risk of CRC (Ollberding et al. 2012). Thus, gene–environment interaction studies do not support a strong role of HCAs in the aetiology of CRC.

PTGS2 (encoding COX-2) is induced by inflammatory stimuli (Wang and DuBois 2010a, b). COX enzymes catalyse the rate-limiting conversion of arachidonic acid to prostaglandins such as the pro-inflammatory and pro-carcinogenic prostaglandin E_2 (PGE₂) (Wang and DuBois 2010a, b; Bacchi et al. 2012). In this review, we found that individuals carrying the G-765C C-variant allele were at high risk of CRC by the intake of meat in contrast to the homozygous wild-type carriers (Andersen et al. 2013a, b). The functional effect of the *PTGS2* G-765C polymorphisms is not clear as studies have found higher as well as lower activity associated with the variant (Papafili et al. 2002; Brosens et al. 2005; Zhang et al. 2005). In Danes, the *PTGS2* G-765C-variant allele is in tight linkage with the *PTGS2* T8473C-variant allele (Andersen et al. 2011b). The microRNA Mir-542-3p targets *PTGS2* mRNA for decay through binding to the T8473C wild-type allele, whereas the variant allele disrupts the binding leading to increased

half-life of the *PTGS2* mRNA (Moore et al. 2012). This finding suggests that carriers of the variant alleles of these polymorphisms have a genetically determined high level of *PTGS2* mRNA. On the other hand, no interaction was found between the *PTGS2* T8473C polymorphism and meat intake in the same study (Andersen et al. 2013a, b). Thus, the biological implication of *PTGS2* on meat carcinogenesis is not readily interpretable.

ABCB1, *ABCC2*, and *ABCG2* encode the ATP-binding cassette (ABC) transport proteins ABCB1 (also called MDR1 and P-glycoprotein), ABCC2 and ABCG2, respectively. The ABC transporters have been found to transport a wide variety of compounds over the cell membrane, including amino acids, peptides, ions, metabolites, vitamins, fatty acid derivatives, steroids, organic anions, phospholipids, drugs, and other exogenous compounds (Quazi and Molday 2011; Coleman et al. 2013; Tarling et al. 2013). Specifically, ABCB1 has been associated with transport of endogenous pro-inflammatory signal substrates such as IL and LT (Johnstone et al. 2000; Pawlik et al. 2005a, b; Mizutani et al. 2008), whereas ABCC2 was found to transport diet- and smoke-derived carcinogens (Dietrich et al. 2001; Jedlitschky and Keppler 2002; Haimeur et al. 2004; Deeley and Cole 2006). In this review, we found that carriers of *ABCB1* C3435T homozygous wild-type and intron 3 G-rs3789243-A-variant allele were at high risk of CRC, whereas carriers of the other alleles were unaffected by meat intake. The silent *ABCB1* C3435T polymorphisms have been reported to change transport specificity and protein stability (Fung and Gottesman 2009; Fung et al. 2014), whereas the intron 3 G-rs3789243-A-variant allele has been associated with low *ABCB1* mRNA level in the intestine, thus suggesting that low level of *ABCB1* is a risk factor for CRC when eating meat (Andersen et al. 2013c). The release of IL-2, IL-4, interferon gamma, and tumour necrosis factor-alpha from activated peripheral blood mononuclear cells was found to be significantly lower among carriers of the homozygous T-variant allele of *ABCB1* C3435T compared to the carriers of the wild-type allele (Johnstone et al. 2000; Pawlik et al. 2005a, b; Mizutani et al. 2008). Thus, the results therefore suggest that genetically determined low *ABCB1* level disposes for CRC when eating meat.

Cytokines such as the pro-inflammatory IL-1B and the anti-inflammatory IL-10 are mediators of inflammation in the intestine (Coussens and Werb 2002). In this review, we found interaction between meat intake and the marker polymorphism near *IL10* rs3024505. The functional effects of rs3024505 are not known, so the interpretation of the possible biological impact in relation to meat carcinogenesis was not possible. In this review, we found no interaction between *IL1B* and meat intake, suggesting that *IL1B* is not involved in meat carcinogenesis in relation to CRC.

Transcription factors bind to DNA sequences, thereby regulating the transcription process for the targeted genes. Pregnane X receptor (PXR) and liver X receptor (LXR) are members of the nuclear receptor superfamily that regulate responses to xenobiotic exposure and lipid homeostasis, respectively (di Masi et al. 2009; McEwan 2009). Nuclear factor-kappa B (NFκB) is involved in inflammatory response, apoptosis, and cell proliferation (Seufert et al. 2013). In this review, we found that carriers of the *NFKB1* -94ins/del del-variant alleles were at high risk of CRC, whereas homozygous wild-type allele carriers had no risk by eating meat. The -94 del-variant was found to be associated with low transcription of *NFKB1* p50 in a luciferase reporter system (Karban et al. 2004). Hence, the deletion allele leads to lower levels of the p50 subunit of NFκB. This would lead to preferential depletion of the anti-inflammatory p50 dimer of NFκB, which, in turn, may lead to a relative overweight of the pro-inflammatory effects of NFκB. The results of this review therefore suggest that carriers of the *NFKB1* -94ins/del del-variant allele were at high risk of CRC due to genetically determined high inflammatory response.

Heme iron has been associated with cell proliferation in intestinal mucosa (Santarelli et al. 2008; Ferguson 2010; Alexander and Cushing 2011; Alexander et al. 2011; Erridge 2011; Zur 2012). Also, heme in red meat has been found to stimulate the production of mutagenic NOC (Joosen et al. 2009). Heme oxygenase-1 (encoded by *HMOX1*) is the rate-limiting enzyme in the degradation of heme to carbon monoxide (CO), iron, and biliverdin, thereby reducing cellular oxidative stress and inhibiting pro-inflammatory cytokines (Oates and West 2006). *HMOX1* A-413T (rs2071746) polymorphism affects heme oxygenase-1 activity (Ono et al. 2004). The assessment of interactions between meat intake and functional polymorphisms in *HMOX1* may therefore indicate whether heme or heme iron contributes to CRC risk (Tappel 2007). In this review, we found no interactions between the functional *HMOX1* A-413T (rs2071746) polymorphism and meat intake in relation to CRC. Thus, the results suggest that neither heme nor heme iron is a strong risk factor for CRC.

Meat, particularly processed meat, contains mutagens such as NOC, HCAs, and PAHs, which may increase the risk of CRC among persons with genetically determined low DNA repair capacity (Santarelli et al. 2008; Ferguson 2010; Alexander and Cushing 2011; Alexander et al. 2011; Erridge 2011; Zur 2012). Mismatch repair primarily corrects single base-pair mismatches and small insertion-deletion loops that arise during DNA replication (Berndt et al. 2007). The nucleotide excision repair (NER) pathway is the primary mechanism for repair of bulky DNA adducts and thus is an important part of the cellular defence against

a large variety of structurally unrelated DNA lesions (Hansen et al. 2007). In this review, interactions between *MSH3* and *XPC* involved in DNA repair and meat in relation to CRC were suggested in prospective studies. Furthermore, interactions between the *XPC* Lys939Gln/K939Q and red meat intake were found in two independent cohorts (Table 1 and S1). Steck et al. found increased risk by high well-done red meat intake among *XPC* Lys939Gln homozygous wild-type carriers in a case-control study, whereas Sorensen in a prospective study found increased risk by red meat intake among the homozygous variant carriers compared to the homozygous wild-type carriers with low meat intake (reference group) (Hansen et al. 2007; Steck et al. 2014). Thus, the finding in the prospective cohort was not replicated in the case-control cohort. The different direction of the risk estimates between the two studies may be due to varying linkage of the *XPC* Lys939Gln polymorphism with functional polymorphisms within the same gene between the two studied populations (Aissani 2014). The functional implication of this polymorphism is not clear (Zhu et al. 2014). Thus, although the functional implications of the *XPC* polymorphism are difficult to interpret, the results suggest that meat intake leads to the formation of DNA adducts and that this mechanism is involved in meat carcinogenesis.

Some of the findings in this review point to the same underlying mechanisms. *PTGS2*, *IL10*, *ABCB1*, and *NFKB1* are all involved in the intestinal immune response, thus suggesting the involvement of the inflammatory response in meat-related carcinogenesis. Furthermore, the use of functional polymorphisms enables a biological interpretation of the interactions of *ABCB1* and *NFKB1* with meat. Interaction analyses indicated that meat intake selectively increased the risk of CRC among carriers of the *NFKB1* del-variant allele associated with high pro-inflammatory activity and among the carriers of the *ABCB1* allele associated with functional release of pro-inflammatory molecules from activated immune cells (Karban et al. 2004; Pawlik et al. 2005a, b). Therefore, these results suggest that genetically determined high inflammatory response is involved in meat colorectal carcinogenesis. Also, the suggested interaction with *MSH3* and *PXC* supports a role of DNA adducts in meat carcinogenesis. The results of this review together with recent findings thereby suggest a link between meat intake and cancer via intestinal inflammation and DNA damage (Carbonero et al. 2012; Devkota et al. 2012; Jia et al. 2012). Also, negative findings may provide important information. The present study did not support a strong role of heme, iron, and HAC cooking carcinogens in the aetiology of CRC.

The limitations of this review were derived from heterogeneity and the known large variability in meat intake

and meat cooking methods between the included studies. The included case-control studies are hampered by recall bias. Recall bias may severely affect the quality of the self-reported data making the use of objective data or prospectively self-reported data desirable. Large prospective studies are needed in order to have sufficient power to assess gene-environment interactions. Also, the meat intake should be high and sufficiently distributed among the participants in the studied cohort. Seven of the eleven prospective studies were performed in the Danish “Diet, Cancer and Health” cohort, and Danes have a high meat intake compared with low-income countries. For example, *NFKB1* was associated with CRC in a Swedish cohort but not in a Chinese (Lewander et al. 2007). The results from the Danish study suggest that interaction between meat intake and *NFKB1* may be part of the reason why *NFKB1* was associated with CRC in the Swedish cohort with a high meat intake but not among Chinese who have a low intake of meat. In addition, the careful selection of functional polymorphisms or subsequent functional characterisation of polymorphisms is of most importance if biological interpretation is to be performed. Because the analyses were based on biologically funded hypothesis, we used a *P* value for the interaction of 0.05 as significance level. Traditionally, carcinogens are identified using a combination of animal studies and epidemiological studies (IARC 2014). Gene-environment interactions should be regarded a complementary approach which may prove a useful way of identifying the combinations of environmental factors and biological pathways in carcinogenesis. Future studies should aim at assessing multiple functional polymorphisms in biological pathways or networks hypothesised to affect meat carcinogenesis using large well-characterised prospective cohorts with relevant meat exposure.

All in all, we found indications from prospective studies that meat interacts with polymorphisms in *PTGS2*, *IL10*, *ABCB1*, *NFKB1*, *XPC*, and *MSH3*, but not *IL1B*, *HMOX1*, *ABCC2*, *ABCG2*, *NR1I2*, *NR1H2*, *NAT1*, *NAT2*, *MSH6*, or *MLH1* in relation to CRC (Table 1). However, none of the found interactions were replicated.

Conclusion

The results from this systematic review suggest that genetic variation in the inflammatory response and DNA repair is involved in meat-related colorectal carcinogenesis, and no support for the involvement of heme and iron from meat or cooking mutagens was found. However, none of the found interactions had been replicated. Further studies of the biological effects by meat intake in relation to CRC are highly warranted.

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Conflict of interest Prof. Vogel declares no conflicts of interest. Dr. Andersen receives compensation as a consultant for MSD and Janssen.

Ethical standard This article does not contain any studies with human or animal subjects performed by the any of the authors.

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