NUTRITION REVIEWS 70 YEARS 1942-2012

Evaluating the links between intake of milk/dairy products and cancer

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Milk and dairy products are widely recommended as part of a healthy diet. These products, however, can contain hormones such as insulin-like growth factor 1, and some studies have suggested that a high intake of milk and dairy products may increase the risk of cancer. This review examines recent studies on this topic, with the evidence suggesting that the recommended intake of milk and dairy products (3 servings/day) is safe and, importantly, does not seem to increase the risk of cancer. On the basis of the studies included in this review, cultured milk, yogurt, and low-fat dairy products should be preferred as the milk and dairy products of choice.

INTRODUCTION

Milk and dairy products have constituted part of the dietary pattern of humans since ancient times and have been widely recommended as part of a healthy diet for many centuries. They represent the best source of dietary calcium and are also good sources of protein, phosphorus, magnesium, and fat-soluble vitamins.

Technological advances have led to the development of several different types of milk and dairy products, thereby increasing the availability of these products to populations with different dietary patterns and needs. According to the International Dairy Federation, in 2006 the per capita consumption of fluid milk was 83.9 liters in the United States, 92.6 liters in the European Union, and 8.8 liters in China.[1] According to US Department of Agriculture data, the per capita milk and cream consumption in the United States declined from 28.5 gallons per year in 1980 to 23.5 gallon per year in 2009.[2] One reason for this decrease in milk and dairy product consumption could be related to the possible link between these products and increased risk of some types of cancer. Furthermore, it has been demonstrated that dairy products sometimes contain hormones such as insulin-like growth factor 1 (IGF-1), which is recognized to have negative effects on health.[3] The aim of the present study is to present the evidence linking IGF-1 to the development of cancer and to review recent studies in humans that evaluated the role of milk and dairy product consumption on the incidence of cancer.

MILK, DAIRY PRODUCTS, AND INSULIN-LIKE GROWTH FACTOR 1

Cow's milk contains various bioactive hormones, including insulin-like growth factor 1 (IGF-1) and insulin-like growth factor 2 (IGF-2). The high concentration of IGF-1 (4–50 ng/mL) and IGF-2 (40–50 ng/mL) in cow's milk is related to recombinant growth hormone, which is administered to cows to increase milk production.[3] The consumption of cow's milk by humans promotes an increase in the plasmatic concentration of the bioactive form of IGF-1. This increase is related to the presence of casein in milk, which promotes the intestinal absorption of this hormone. In addition, milk-borne IGF-1 absorbed from the bowels into the bloodstream may exert its effects in liver and other peripheral tissues.[4] Depending on the amount of milk consumed, an increase in the serum concentration of IGF-1 occurs after milk ingestion, ranging from 10% to 20% in adults and from 20% to 30% in children.

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Key words: dairy, diet, health

doi:10.1111/j.1753-4887.2012.00464.x

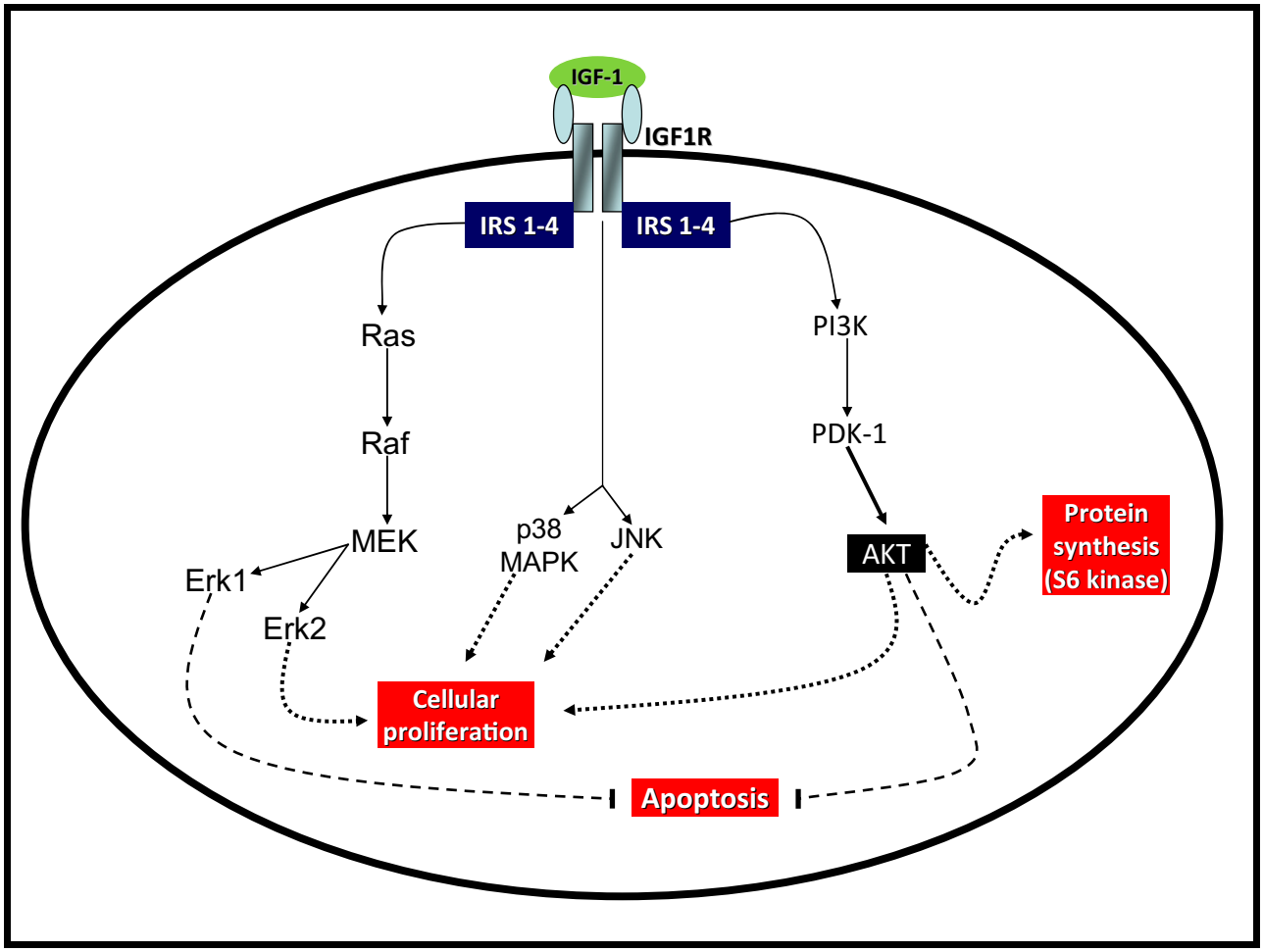

Figure 1 **The insulin growth factor 1 receptor (IGF1R)-mediated signal transduction pathway.** *Abbreviations:* Akt, protein kinase B; Erk, extracellular signal related kinase; IGF-1, insulin-like growth factor 1; IGF1R, insulin-like growth factor receptor 1; IRS, insulin receptor substrate; JNK, c Jun N terminal kinase; MEK, MAP kinase kinase; PDK-1, 3-phosphoinositide-dependent kinase-1; PI3K, phosphatidylinositol-3`-kinase; Raf, MAP kinase kinase kinase (MAP3K); Ras, guanosine-nucleotide-binding protein.

The consumption of cow's milk increases the serum concentration of IGF-1 in the perinatal period, during adolescence, and in adulthood, whereas during puberty, a period associated with a physiological increase in the secretion of growth hormone (GH), the serum concentration of IGF-1 increases and is further enhanced by milk consumption.[5,6] It should be noted that the consumption of milk protein induces postprandial hyperinsulinemia and shifts the GH/IGF-1 axis to permanently increased IGF-1 serum levels.[7]

In a recent systematic literature review that summarized and quantified the current findings on dairy product consumption and its effect on the serum concentration of IGF-1, only three of 12 studies reported a statistically positive correlation between dairy product consumption and IGF-1 serum concentrations.[8] It should be noted that IGF-1 in milk is less affected by homogenization and pasteurization than by the processing of milk to dairy products[9]; either IGF-1 in milk or a substance in milk that can stimulate endogenous production of IGF-1 can be inactivated during such processing.[10]

IGF-1 and GH play critical roles in the regulation of growth and in the homeostasis of various tissues.[11] GH has the ability to regulate IGF-1 synthesis, since, in the liver, GH stimulates the synthesis and secretion of IGF-1, which is an important mediator of cellular growth. The insulin-like growth factor system consists of the following: the three ligands, insulin, IGF-1, and IGF-2; the three corresponding high-affinity receptors, insulin-R, IGF-1R, and IGF-2R; the six IGF-binding proteins, IGFBP-1 to -6, that associate with the high-affinity IGFs; and the nine IGFBP-related proteins, IGFBP-rP1 to 9, that bind to IGFs with approximately tenfold lower affinity compared with the high-affinity IGFBPs. Regarding IGF-1, it has been found that over 90% of this hormone in plasma is bound to IGF-binding protein 3 (IGFBP-3), with the remainder

being bound to IGFBP-1, -2, -4, and -6. IGF-1 receptor (IGF-1R) mediates signal transduction. Due to its tyrosine kinase activity, IGF-1R is capable of forming a heterodimer with the insulin receptor. It is worth noting that insulin binds primarily to its receptor, although this hormone can be bound, with low affinity, to IGF-1R. In addition, IGF-1 and IGF-2 may also have a capacity for low-affinity binding to insulin receptor. It should also be pointed out that human and bovine IGF-1 are identical and can be bound with the same affinity to IGF1R.[12,13]

The IGF-1R-mediated signal transduction pathway primarily activates the Ras/Raf/MAP kinase signaling cascade while simultaneously activating the phosphoinositol-3-kinase signaling pathway, which promotes cellular proliferation, lipogenesis, and growth while at the same time inhibiting apoptosis (Figure 1). Since IGF-1 stimulates growth and differentiation and inhibits apoptosis, this hormone may influence the development of tumors.[13,14] In addition, several studies show a correlation between elevated serum concentrations of IGF-1 and increased prevalence of breast, prostate, and colorectal cancer.[15–17]

Besides IGF-1, cow's milk also contains the 5alpha-reduced compound 5alpha-pregnanedione, which is a direct precursor of dihydrotestosterone, which is involved in the genesis of prostate cancer. At the same time, 5alpha-pregnanedione has been shown to induce estrogen receptors in breast cancer cells, thereby upregulating the sensitivity of cancer cells to estrogen.[18]

MILK, DAIRY PRODUCTS, AND CANCER

Information about the association between consumption of milk and dairy products and cancer is extensive.[19] Recent human studies and meta-analyses evaluated the relationship between milk/dairy intake and the risk of developing several malignancies. By considering the evidence that diet or certain dietary compounds could affect circulating IGF-1 in Western populations,[8] the present review focuses on the association between the consumption of milk and dairy products and the better-elucidated types of cancer in which such a relationship has been observed, such as bladder, prostate, breast, and colon cancers.

Human studies investigating the association between milk/dairy product consumption and the development of bladder cancer are listed in Table 1. In general, both case-control and cohort studies suggested that the recommended consumption of milk and dairy products (3 servings/day) is safe and does not increase the risk of bladder cancer. In a Swedish cohort study, there were no differences in the incidence of bladder cancer between subjects who consumed 7 or more servings/day of dairy products compared with subjects who consumed <3.5

Table 1 **Summary of human studies that evaluated the role of milk/dairy product consumption in the development of bladder cancer.**

Study	Country	Study design and number of subjects enrolled	Impact on incidence of bladder cancer
Radosavljevic et al. (2003)[20]	Serbia	Case-control; 130 cases and 130 controls	Skim milk: OR 0.27; 95% CI 0.16–0.91 Yogurt: OR 0.34; 95% CI 0.12–0.97
Hemelt et al. (2010)[21]	China	Case-control; 432 cases and 392 controls	Daily consumption of milk: OR 0.49; 95% CI 0.32–0.76 More than 1 cup of milk/day: OR 0.30; 95% CI 0.13–0.72
Sakauchi et al. (2004)[22]	Japan	Cohort; 47,997 men and 66,520 women followed up for 9–11 years	Milk consumption: 4× versus 1× per week (OR 0.65; 95% CI 0.36–1.18). Almost every day (OR 0.47; 95% CI 0.28–0.81). *P* for trend 0.006
Larsson et al. (2008)[23]	Sweden	Cohort; 82,002 women and men	No association with total dairy intake Cultured milk: RR 0.62; 95% CI 0.46–0.85 for ≥2 servings/day compared with no servings
Keszei et al. (2010)[24]	Netherlands	Cohort; 120,852 men and women followed up for 16.3 years	Dairy intake: HR 1.01; 95% CI 0.81–1.27, *P* for trend 0.68 Butter: HR 1.61; 95% CI 1.03–2.5; *P* for trend <0.01
Ursin et al. (1990)[25]	Norway	Cohort; 15,914 women followed up for 11.5 years	≥2 glasses of milk/day compared with <1 glass/day: OR 0.56; *P* value 0.02
Chyou et al. (1993)[26]	USA	Cohort; 7,995 Japanese-American men followed up for 22 years	Weak inverse association for milk (*P* value 0.07)

Abbreviations: CI, confidence interval; HR, hazard ratio; OR, odds ratio; RR, relative risk.

Table 2 **Summary of human studies that evaluated the role of milk/dairy product consumption in the development of prostate cancer.**

Study	Country	Study design and number of subjects enrolled	Impact on incidence of prostate cancer
Bosetti et al. (2004)[27]	Italy	Case-control; 1,294 cases and 1,451 controls	Milk and dairy intake: OR 1.2 for 14 servings/week versus no servings/week No difference between whole milk, partially skimmed milk, skimmed milk, or yogurt
Torniainen et al. (2007)[28]	Sweden and Finland	Case-control; 4,153 cases and 2,315 controls	Low-fat milk: OR 1.73; 95% CI 1.16–1.39
Raimondi et al. (2010)[29]	Canada	Case-control; 197 cases and 197 controls	Total dairy intake: OR 2.19; 95% CI 1.22–3.94 for >468.9 g/day compared to <117.3 g/day Milk was the only dairy product positively associated: OR 2.27; 95% CI 1.25–4.09 for >408 g/day versus <117 g/day
Kesse et al. (2006)[30]	France	Cohort; 2,776 men	Dairy products: RR 4th quartile versus 1st quartile 1.35; 95% CI 1.02–1.78; *P* value 0.04 Yogurt: Increment of 125 g/day: RR 1.61; 95% CI 1.07–2.43; *P* value 0.02
Koh et al. (2006)[31]	USA	Cohort; 10,011 men	Dairy products: RR 1.05; 95% CI 0.84–1.31
Mitrou et al. (2007)[32]	Finland	Cohort; 29,133 men	Total dairy intake not associated with prostate cancer after an adjustment for calcium (*P* for trend 0.17)
van der Pols et al. (2007)[33]	England and Scotland	Cohort; 4,383 children followed up from 1937–1939 to 2005	No association with dairy intake Weak inverse association with high milk intake (>282 mL/day) during childhood (*P* for trend 0.11)
Rohrmann et al. (2007)[34]	USA	Cohort; 3,892 men	Dairy products: ≤1 serving/week compared with >5 servings/week (HR 1.65; 98% CI 1.02–2.66)
Kurahashi et al. (2010)[35]	Japan	Cohort; 43,435 men followed up for 7.5 years	RR for the highest versus the lowest quartiles of total dairy products, milk, and yogurt were 1.63 (95% CI 1.14–2.32), 1.53 (95% CI 1.07–2.19), and 1.52 (95% CI 1.10–2.12), respectively
Ahn et al. (2007)[36]	USA	Cohort; 29,509 men	Low-fat dairy products (>2.75 servings/day): RR 1.12; 95% CI 0.97–1.30
Park et al. (2007)[37]	USA	Cohort; 293,888 men	≥2 versus no servings of skim milk: RR 1.23; 95% CI 0.99–1.54; *P* for trend 0.01
Park et al. (2007)[38]	USA	Cohort; 82,483 men followed for 8 years	No association with dairy and milk intakes

Abbreviations: CI, confidence interval; HR, hazard ratio; OR, odds ratio; RR, relative risk.

servings/day.[23] Importantly, some of these studies even showed a protective effect associated with an increase in the consumption of dairy products.[20–22,25] When the effect of individual dairy products was isolated, milk and yogurt seemed to provide dose-dependent protection,[21–23,25] while cheese was not associated with the development of bladder cancer.[22–24] Despite the lack of information regarding the role of fat and non- or low-fat dairy products in bladder cancer, a Dutch cohort study found butter consumption to be positively associated with bladder cancer.[24]

Table 2 presents an overview of human studies that investigated the association between consumption of milk/dairy products and the development of prostate cancer. Classically, the consumption of these products is associated with an increased risk of prostate cancer,[27] but the increase in risk seems to be small.[39] The negative effect of milk/dairy product consumption on prostate cancer seems to be related to its major constituent: calcium.[40,41] However, calcium intake was not associated[34] or was only marginally associated with prostate cancer risk.[29,38] Similarly, in Asia, where the major source of dietary calcium is vegetables, a modest nonsignificant increase in prostate cancer was also found in association with an increase in calcium intake.[42]

Some recent studies also investigated a possible association between other dairy components, such as phosphate[43] and phytanic acid,[44] and prostate cancer, but it is premature to draw conclusions from the evidence obtained to date. Based on present knowledge, the asso-

Table 3 **Summary of human studies that evaluated the role of milk/dairy product consumption in the development of breast cancer.**

Study	Country	Study design and number of subjects enrolled	Impact on incidence of breast cancer
Bessaoud et al. (2008)[45]	France	Case-control; 437 cases and 922 controls	Dairy consumption: OR 1.57; 95% CI 1.06–2.32 for 134.3 g/day and 271.2 g/day versus <134.3 g/day
Zhang et al. (2011)[46]	China	Case-control; 438 cases and 438 controls	Consumption of dairy products was not associated with breast cancer
Kesse-Guyot et al. (2007)[47]	France	Cohort; 3,627 women	Consumption of dairy products: whole population (RR 0.55; 95% CI 0.29–1.03; *P* for trend 0.03); in premenopausal women (RR 0.35; 95% CI 0.12–0.95; *P* for trend 0.01)
Linos et al. (2010)[48]	USA	Cohort; 39,268 premenopausal women in the Nurses Health Study II	No association between total dairy and milk intake and incidence of breast cancer
Hjartaker et al. (2010)[49]	Norway	Cohort; 64,904 women followed from 1996/1999 through 2006	Consumption of white cheese ≥25.3 g/day: HR 0.5; 95% CI 0.29–0.87; *P* for trend 0.02 compared with those who consumed <6 g/day. Consumption of whole milk ≥2.5 g/day: HR 1.39; 95% CI 0.87–2.23; *P* for trend 0.06 compared with those who consumed <0.3 g/day
Pala et al. (2009)[50]	Europe	Cohort; 319,826 women	Dairy products were not a risk factor for breast cancer. Butter consumption: HR 1.28; 95% CI 1.06–1.53; *P* for trend 0.21 for the highest compared with the lowest quintile in premenopausal women
Hjartaker et al. (2001)[51]	Norway	Cohort; 48,844 premenopausal women followed up for 6.2 years	Intake of ≥3 glasses of milk/day: incidence rate ratio of breast cancer 0.56 compared with women who did not drink milk. Childhood and adulthood milk consumption: negative trend in breast cancer incidence
Ursin et al. (1990)[25]	Norway	Cohort; 15,914 women followed up for 11.5 years	Intake of ≥2 glasses of milk/day compared with <1 glass/day (OR 1.48; *P* value 0.40)

Abbreviations: CI, confidence interval; HR, hazard ratio; OR, odds ratio; RR, relative risk.

ciation between milk/dairy products and prostate cancer is not yet fully understood. The studies performed thus far vary in their attention to methodological details such as age and cancer stage; moreover, clear evidence of a dose-response relationship has not been established. Therefore, considering calcium is an essential nutrient, the recently revisited recommendation for dietary calcium intake may be considered safe.

In general, a higher level of milk and dairy product consumption is safe and is inversely associated with breast cancer (Table 3). When dairy product consumption was examined separately from other factors, milk provided a stronger protective effect. Two Norwegian cohort studies[49,51] highlight that premenopausal women who had a high consumption of milk had a lower risk of developing breast cancer when compared with women who had low milk consumption or did not consume milk. Despite the lack of evidence, low-fat milk/dairy products seem to offer a more protective effect than whole milk or butter. In a Norwegian cohort study, premenopausal women with the highest consumption of white cheese had half the risk of developing breast cancer when compared with those who had the lowest consumption.[49] Nevertheless, there was a positive trend for breast cancer with increased consumption of fat from milk,[49] and in a European cohort study, breast cancer risk in premenopausal women was positively associated with butter consumption.[50]

The incidence of colon cancer is reduced in subjects with high and regular consumption of milk/dairy products (Table 4). In two cohort studies, the protective effect observed was dose dependent.[55,56] Although information is scarce regarding colon cancer incidence relative to the consumption of high-fat as well as non- and low-fat milk and dairy products, a Swedish cohort study reported that women with the highest consumption of high-fat dairy products had a lower risk of colon cancer when compared with women who had the lowest consumption.[56] It was

Table 4 **Summary of human studies that evaluated the role of milk/dairy product consumption in the development of colon cancer.**

Study	Country	Study design and number of subjects enrolled	Impact on incidence of colon cancer
Magalhães et al. (2011)[52]	Portugal	Case-control; 102 cases and 879 controls	Higher risk of colorectal cancer among subjects with low consumption of milk and dairy products
Hubner et al. (2008)[53]	United Kingdom	Clinical trial; 853 men and women	The RR of colorectal adenoma recurrence in subjects in the highest tertile of milk intake (>427.5 mL/day) was half that of subjects in the lowest tertile (<285 mL/day)
Lee et al. (2009)[54]	China	Cohort; 73,224 women followed up for 7.4 years	Milk: RR 0.52; 95% CI 0.38–0.72; *P* for trend 3.2×10^{-5} from 0 to ≥200 g/day
Larsson et al. (2006)[55]	Sweden	Cohort; 45,306 men aged 45–79 years followed up for 7 years	Total dairy products: RR for ≥7 servings/day versus <2 servings/day was 0.46 (95% CI 0.30–0.71; *P* for trend 0.01)
Larsson et al. (2005)[56]	Sweden	Cohort; 60,708 women aged 40–76 years followed up for 14.8 years	High-fat dairy products: RR >4 servings versus <1 serving/day was 0.59 (95% CI 0.44–0.79; *P* for trend 0.002) Each increment of 2 servings/day: 13% reduction in risk
Pala et al. (2011)[57]	Italy	Cohort; 14,241 men and 31,063 women followed up for 12 years	Yogurt is protective: HR 0.65 (95% CI 0.48–0.89) in the highest versus the lowest tertile

Abbreviations: CI, confidence interval; HR, hazard ratio; RR, relative risk.

suggested that the protective effect of milk and dairy products on colon cancer is related to certain components such as butyric acid and fermentation products.[58] Thus, although information regarding the role of specific dairy products is lacking, fermented milk and yogurt seem to provide a protective effect.

CONCLUSION

In summary, although some studies suggest that milk and dairy products affect the IGF-1 pathway,[9–12] the present review indicates that the recommended intake of milk and dairy products (3 servings/day) can be considered safe. Importantly, the consumption of milk and dairy products does not consistently increase the risk of prostate cancer and seems to be protective against bladder, breast, and colon cancers.

A notable problem in assessing the evidence is the considerable variation in how consumption data were collected, with some studies reporting overall dairy product consumption while others reported categories such as milk, butter, cheese, and cultured milk as well as full-fat or nonfat milk and dairy products. However, among all dairy products available, cultured milk, yogurt, and low-fat dairy products seem to be better choices for providing nutrients to prevent not only cancer but other chronic diseases as well.

Cancer is an extremely complex disease associated with both lifestyle factors and genetic/epigenetic changes. Thus, the role of milk and dairy product consumption on cancer might be modified by genetic background. Accordingly, the reduction in the risk of colorectal adenoma recurrence associated with a high intake of dairy products was confined to the vitamin D receptor genotype.[54] Therefore, future studies designed to evaluate the influence of genetics on the association between dairy product consumption and cancer development could expand existing knowledge and provide new insight into the role of nutrition in the risk and prevention of cancer.

Acknowledgments

All authors contributed equally to this manuscript. C.E.A.C is a postdoctoral fellow from the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP n°2010/08386-7).

Declaration of interest. The authors have no relevant interests to declare.

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