Roles of Caloric Restriction, Ketogenic Diet and Intermittent Fasting during Initiation, Progression and Metastasis of Cancer in Animal Models: A Systematic Review and Meta-Analysis

Mengmeng Lv¹,²*, Xingya Zhu³,⁴*, Hao Wang⁴, Feng Wang⁴, Wenxian Guan⁴*

¹. Department of General Surgery, Nanjing Medical University Affiliated Cancer Hospital, Cancer Institute of Jiangsu Province, Nanjing, China, ². The First Clinical School of Nanjing Medical University, Nanjing, China, ³. Gulou Clinical Medical College, Nanjing Medical University, Nanjing, China, ⁴. Department of Gastrointestinal Surgery, Nanjing Gulou Hospital Affiliated to Medical College of Nanjing University, Nanjing, China

Abstract

Background: The role of dietary restriction regimens such as caloric restriction, ketogenic diet and intermittent fasting in development of cancers has been detected via abundant preclinical experiments. However, the conclusions are controversial. We aim to review the relevant animal studies systematically and provide assistance for further clinical studies.

Methods: Literatures on associations between dietary restriction and cancer published in PubMed in recent twenty years were comprehensively searched. Animal model, tumor type, feeding regimen, study length, sample size, major outcome, conclusion, quality assessment score and the interferential step of cancer were extracted from each eligible study. We analyzed the tumor incidence rates from 21 studies about caloric restriction.

Results: Fifty-nine studies were involved in our system review. The involved studies explored roles of dietary restriction during initiation, progression and metastasis of cancer. About 90.9% of the relevant studies showed that caloric restriction plays an anti-cancer role, with the pooled OR (95%CI) of 0.20 (0.12, 0.34) relative to controls. Ketogenic diet was also positively associated with cancer, which was indicated by eight of the nine studies. However, 37.5% of the related studies obtained a negative conclusion that intermittent fasting was not significantly preventive against cancer.
Conclusions: Caloric restriction and ketogenic diet are effective against cancer in animal experiments while the role of intermittent fasting is doubtful and still needs exploration. More clinical experiments are needed and more suitable patterns for humans should be investigated.

Introduction

Cancer was the second leading cause of mortality worldwide and its incidence has been increasing during the last decades [1, 2]. Epidemiological studies report that diet plays an important role in the initiation, promotion and progression of common cancers [3]. For centuries, dietary restriction has been widely recognized with health benefits and consistently been shown to extend lifespan in various mammals [4, 5]. Its anticancer effects have recently been identified via numerous animal experiments. Among various dietary restriction regimens, caloric restriction (CR), intermittent fasting (IF) and carbohydrate restriction/ketogenic diet (KD) are the most studied methods that are beneficial for cancer prevention.

CR prevents tumorigenesis by decreasing metabolic rate and oxidative damage [2]. The mechanism behind IF is relatively simple: it postpones tumor growth by starving tumors from glucose for a short period [6]. KD used to treat refractory seizures in children for decades is a diet regimen composed of low carbohydrates (usually less than 50 g/day), high fat and enough proteins. KD can restrict glucose for ATP production and energy derivation in cancer cells [6–8].

The present results chiefly originate from animal models, such as spontaneous model, chemical induced model, transgenic model and transplanted model [9]. Since human clinical trials of dietary restriction are extremely rare, it is urgent to review the existing achievements regarding the cancer preventive efficacy of dietary restriction in animal models. The present systematic review was conducted to discuss the findings from the most relevant and recent studies concerning the effects of dietary restriction regimens on cancer prevention.

Methods

Literature search and inclusion criteria

Keywords including “calorie restriction”, “caloric restriction “, “intermittent fasting”, “carbohydrate restriction”, “ketogenic diet”, “cancer” and “tumor” on Pubmed published between 1994 to January 2014 were searched, with limitation to English language. The inclusion criteria are: 1. studies on the anticancer effects of CR, IF or KD; 2. studies using animal models; 3. studies reporting at least one of the outcome measures associated with antitumor effects. Studies in vitro and on human participants were excluded. Repeated studies performed by the same author would not be included.
The titles and abstracts of the obtained articles were reviewed by two reviewers (M.M.L. and X.Y.Z.) independently. After excluding the articles not meeting the inclusion criteria, the two reviewers read the whole passage of the remaining articles to make sure they truly met the inclusion criteria. Any controversy was resolved by discussion with the third reviewer (H.W.) to reach consensus amongst all reviewers.

Quality assessment and data extraction
Two reviewers (M.M.L. and X.Y.Z.) independently appraised each included article according to a critical checklist of the Stroke Therapy Academic Industry Roundtable (STAIR) [10]. The key points of this checklist include: 1. performing appropriate sample size calculations; 2. defining inclusion/exclusion criteria a priori; 3. reporting the generation of stochastic sequence; 4. providing the method of concealing random allocation sequence; 5. reporting the reasons for excluding animals from the final data analysis; 6. eliminating outcome assessment bias; 7. declaring relevant conflicts of interest.

Two reviewers (M.M.L. and X.Y.Z.) independently extracted data. Information including animal model, tumor type, feeding regimen, study length, sample size, major outcome, conclusion, quality assessment score and the interventional step of cancer was extracted from each study using a preset form.

Data analysis
Data were analyzed on Stata 12 (Stata Corporation, College Station, Texas, USA). Dichotomous data were tested using odds ratio (OR) and its 95% confidence interval (CI). Heterogeneity was examined by Chi-square test [11]. A fixed-effects model was used if homogeneity was significant (P>0.1, I²<50%), and otherwise, a random-effects model was used.

Results
Eligible studies
The flow of search strategy is showed (Fig. 1). A total of 1463 articles were identified from Pubmed and 1306 studies were excluded after reviewing title and abstract, with a selection of 157 studies for detailed review. Twenty-three reviews, ten cell experiments, and eight clinical trials were subsequently excluded after full-text reading according to the inclusion criteria. Three republished animal studies, and eight repeated studies performed by the same author were excluded. Fifteen cancer-irrelevant studies were excluded (e.g. obesity, body composition and bone mineral density). Fourteen studies only discussing anticancer mechanisms and eleven studies without providing concrete measures for cancer were also excluded. Three studies studying the effect of agents and three studies with no appropriate control were excluded.
Finally, a total of 59 animal studies fulfilled the inclusion criteria. The characteristics, major outcomes and methodological quality assessment results of each study are given in Table 1, 2, 3. All the included studies used cancer murine models, except for one study evaluating epithelial ovarian cancer (OVAC) preventive strategies which used the chicken model. Spontaneous model, chemical induced model, transgenic model and transplanted model were adopted by the included studies. Two types of hormone-sensitive cancers— breast cancer and prostate cancer were most studied, followed by brain cancer and hepatic cancer. The scores of qualities of the studies using STAIR ranged from 3 to 5.

**CR**

Forty-four included studies that evaluated antitumor effects in animals were placed on CR [12–55] (Table 1). Among them, murine models were most frequently used (43 studies) and chicken model was used in one study. The most studied cancer types were mammary, prostate, brain, pancreatic, and hepatic.
### Table 1. Animal experiments of caloric restriction diet and cancer.

| Author(Year) | Model | Tumor | Feeding Regimens | Sample size | Time | Body weights(g) | Major Results | C | Q | S |
|--------------|-------|-------|------------------|-------------|------|-----------------|---------------|---|---|---|
| Engelman 1994 | Mice  | Mammary, TG | AL; CR (4–12w); CR(continuously) | 60;24;60 | 60 | 42.3; 41.4; 27.8 | Tumor incidence(%): 83; 50; 13 | + | 4 | I |
| Tagliaferro 1996 | Rats  | Mammary, C | AL; Cyclic CR(1w 33% restriction 3w refeeding) | 47;49 | 16 | Cyclic CR<AL | Tumor incidence(%): 54; 66 | - | 4 | I |
| Gillette 1997 | Rats  | Mammary, C | AL; 20%CR | 30;30 | 20.5 | CR<AL | Tumor incidence(%): 23.3; 6.7 | + | 3 | I |
| Pape-Ansorge 2002 | Mice  | Mammary, TG | AL; Cyclic CR(1w 33% restriction 3w refeeding) | 32;31;33 | 80 | 34.9; 31.1; 28.0 | Tumor incidence(%): 37.5; 22.5; 33 | 4 | I |
| Thompson 2004 | Rats  | Mammary, C | AL; 40% CR;AL | 54;24 | 11 | 162;207 | Tumor incidence(%): 59;96 | + | 4 | I |
| Zhu 2005 | Rats  | Mammary, C | AL; ICR(3 weeks 50% CR 3 weeks AL);CCR | 32;31;33 | 80 | 34.9; 31.1; 28.0 | Tumor incidence(%): 37.5; 22.5; 33 | + | 3 | I |
| Thompson 2004 | Rats  | Mammary, C | AL; 40% CR;AL | 54;24 | 11 | 162;207 | Tumor incidence(%): 59;96 | + | 4 | I |
| Zhu 2005 | Rats  | Mammary, C | AL; 40% CR; 6 week 40%CR 8 day refeeding;AL | 30;20;29 | 7 | 139;160;191 | Tumor incidence(%): 56.7;80;96.6 | + | 3 | I |
| Cleary 2007 | Mice  | Mammary, TG | ICR(3 weeks 50% CR 3 weeks AL);CCR; AL | 39;30;31 | 80 | 25/32.5;26.2; 31.2 | Tumor incidence(%): 15;27; 84 | + | 3 | I |
| Jiang 2008 | Rats  | Mammary, C | 20% CR; 40% CR;AL | 30;30;30 | >7 | 150;123;180 | Tumor incidence(%): 60;23;96 | + | 4 | I |
| Dogan 2009 | Mice  | Mammary, TG | ICR(3 weeks 50% CR 3 weeks AL);CCR;AL | 52;40;44 | 64 | 22.6/26.7;25.1;36 | Tumor incidence(%): 11.5;20; 45.5 | + | 5 | I |
| Phoenix 2010 | Mice  | Mammary, TP | 30%CR;AL | / | >27 | / | Tumor volume: CR<AL; Metastases: CR<AL | + | 3 | P, M |
| De Lorenzo 2011 | Mice | Mammary, TP | 40%CR; Normal diet | 7;7 | 9 | 16.6; 21.6 | Wet tumor weight: 1.5; 3.5 g; Metastases: CR<AL | + | 4 | P, M |
| De Lorenzo 2011 | Mice | Mammary, TP | 20% CR; Control diet | 15;15 | 18 | 29.40 | Tumor area: Control diet | 0.04;0.39 g | + | 4 | P |
| Dunlap 2012 | Mice  | Mammary, TP | 30%CR;AL | 20;20 | >42 | / | Tumor area: CR<AL | + | 3 | P |
| Saleh 2013 | Mice  | Mammary, TP | ADF(alternate day feeding); 30%CR; AL | 80(total) | 6 | CR<AL | Tumor growth delay of ADF and CR | + | 4 | P |
| Mizuno 2013 | Mice  | Mammary, TG | CCR; ICR(3 weeks 50% CR 3 weeks AL); AL | 36;29;30 | >50 | CR<AL | Tumor incidence(%): 47; 59; 87 | + | 4 | I |
| Rogozina 2013 | Mice  | Mammary, TG | ICR(3 weeks 50% CR 3 weeks AL);CCR; AL | 45;45;45 | 82 | CR<AL | Tumor incidence(%): 4.4;52.3; 66.7 | + | 4 | I |
| Boileau 2003 | Rats  | Prostate, C | AL; 20%CR | 194 total | >60 | CR<AL | Prostate cancer-free survival: CR>AL | + | 4 | I |
| SUTTIE 2005 | Mice  | Prostate, TP | Late-onset 20%CR; AL | 109(total) | 39 | CR<AL (sex-pluck) | CR retard epithelial lesion development | + | 3 | P |
| Kandori 2005 | Rats  | Prostate, TG | 30%CR; control | 10;10 | 91 | 389.3; 475.2 | Decreased epithelial areas/whole area in CR | + | 4 | I |
| McCormick 2007 | Rats  | Prostate, C | 30%CR; 15%CR;AL | 43;42;43 | 48 | CR<AL | Tumor incidence(%): 72;64;74 | - | 4 | I |
| Bonorden 2009 | Mice  | Prostate, TG | ICR(2 weeks 50% CR 2 weeks AL);CCR; AL | 101;79;41 | 50 | 27.43/ 30.89;29.16; 33.48 | Median time to tumor detection (week): 38;35; 33 | + | 4 | I |
| Blando 2011 | Mice  | Prostate, TG | 30%CR;overweight control; diet-induced obesity | 27;23;23 | 24 | 23.9;40.1;44.9 | Tumor incidence(%): 37;100;100 | + | 4 | I |
| Galet 2013 | Mice  | Prostate, TP | 40% CR; AL | 16;16 | >3 | CR<AL | Tumor weight: 295; 467 mg | + | 4 | P |
Table 1. Cont.

| Author(Year) | Model | Tumor | Feeding Regimens | Sample size | Timea | Body weights(g) | Major Results | Cb | Qc | Sd |
|--------------|-------|-------|------------------|-------------|-------|-----------------|---------------|-----|----|----|
| Seyfried 2003 | Mice | Brain, TP | AL; 40%CR | 7;6 | >2 | CR<AL | Tumor dry weight: CR<AL | + | 3 | P |
| Shelton 2010 | Mice | Brain, TP | 60%CR; AL | 9-10;9-10 | >2 | CR<AL | CR reduced the growth and invasion of tumor | + | 4 | P, M |
| Mulrooney 2011 | Mice | Brain, TP | 30%CR; AL | 5; 4 | >14 | CR<AL | Tumor weight: CR<AL | + | 4 | P |
| Jiang 1997 | Mice | Brain, TP | 10%CR; 20%CR; 40%CR | 35;35;38;33 | 102 | CR<AL | Tumor incidence: 14;9;13;18 | - | 4 | I |
| Birt 1997 | Hamster | Pancreatic, C | AL; 10%CR; 20%CR; 40%CR | 35;35;38;33 | 102 | CR<AL | Tumor incidence: 14;9;13;18 | - | 4 | I |
| Lanza-Jacoby 2013 | Mice | Pancreatic, TG | ICY (1 week 50% CR 1 week AL); CCR; AL | 30;30;30 | >50 | 26.7;35.0;41.4;50 | Tumor incidence(%): 57.7;69;92.3;96 | + | 4 | I |
| James 1994 | Mice | Hepatic, S | AL; 40%CR | 73;72 | 144 | 32.3; 23.5 | Tumor incidence(%): 27.4; 4.2 | + | 4 | I |
| Von Tungeln, 1996 | Mice | Hepatic, C | AL; 40%CR | 46; 42 | 84 | CR<AL | Tumor incidence(%): 41.3; 0 | + | 4 | I |
| Van Ginhoven 2010 | Mice | Skin, C | AL; 40%CR (preoperative); AL | 32;30 | >31 | CR<AL | Papilloma incidence: CR<AL | + | 3 | P |
| Stewart 2005 | Skin, C | 40%CR; AL | 30;30;30 | 10;10 | 22 | 38; 30 | Tumor incidence(%): 40; 20 | + | 3 | I |
| Moore 2012 | Rats | Colonic, C | 30% CR; 15% CR; 10 kcal% fat; 60 kcal% fat | 26;29;27;25 | >50 | 26.7;35.0;41.4;50 | Tumor incidence(%): 57.7;69;92.3;96 | + | 4 | I |
| Tomita 2012 | Rats | Colonic, C | 40%CR; AL | 23;23 | 5 | CR<AL | Number of aberrant crypt foci: CR<AL | + | 4 | I |
| Harvey 2012 | Mice | Colonic, TP | 30%CR; AL | 30;30 | >24 | CR<AL | Tumor volume: CR<AL | + | 4 | P |
| Carver 2011 | Bird | Ovarian, S | 55%CR; full-fed | 394;393 | 2year | 1423;1896 | Tumor incidence(%): 10.3;33.3 | + | 4 | I |
| Mai 2003 | Mice | Intestinal, TG | AL; 40%CR | 30;28 | 9 | CR<AL | Polyp numbers: CR<AL | + | 3 | I |
| Dunn 1997 | Mice | TG | AL; 40%CR | 10;10 | 22 | 38; 30 | Tumor incidence(%): 40; 20 | + | 3 | I |
| Hursting, 1997 | Mice | TG | (P53-); 40%CR(p53-); AL(p53+); 40%CR(p53+) | 28-30/group | 132 | CR<AL | CR delayed tumor mortality relative to AL | + | 4 | I |
| Berrigan 2002 | Mice | TG | AL; 40%CR; 1day/week fast | 31-32/group | >48 | CR<Fast<AL | Tumor free survival: CR>AL; Fast>AL | + | 4 | I |
| Tsao 2002 | Mice | TG | Control; High fat/low calcium; 30%CR | 34;46;16 | / | CR<Control | Intestinal tumor incidence(%): 68; 65; 69 | - | 3 | I |
| Yamazaki 2010 | Mice | TG | 30%CR; AL | 18;17 | >144 | CR<AL | Tumor incidence(%): 16.7; 94.1 | + | 3 | I |

*aTime: Time of study (weeks); bConclusion of the study, “+” indicates a positive conclusion and “-” represents a negative conclusion; cQuality of the study according to a critical checklist of the Stroke Therapy Academic Industry Roundtable; dThe step(s) of cancer that dietary restriction regimens interfere during the initiation, progression and metastasis of cancer; "I" indicates initiation, “P” indicates progression and “M” indicates metastasis; eTG: transgenic; fAL: Ad libitum; CR: caloric restriction; w: week; C: Chemical-induced; ICR: Intermittent caloric restriction; CR: chronic caloric restriction; l: CR mice sacrificed at the end of the 12th restriction period/ICR mice sacrificed at 1 week after 12th refeeding; mTP: transplanted; n: not specified; oLate-onset 20%CR: ad libitum 20 weeks followed by 20% diet restriction; p27.43/30.89: Mice euthanized during restriction/Mice euthanized during AL consumption; q: Spontaneous.

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cancers. Skin, colonic, ovarian and intestinal cancers were also investigated each in one or two related studies. Spontaneous model, chemical induced model, transgenic model and transplanted model were applied. Forty of the forty-four studies (90.9%) supported the positive anticancer role of CR despite the different measurements. Thirty studies investigated the role of CR on initiation of cancer, twenty-six of which addressed the preventive role of CR on cancer initiation. Fourteen studies explored the effect of CR on progression and three of them were also on metastasis of cancer, all of these studies showed that CR modulated progression and metastasis of cancer. The most used measurement was tumor incidence expressed in percentage. Tumor growth, tumor weight and other measurements were also applied. From the included studies, CR tended to be associated with reduced weight comparing to the controls.

Intermittent caloric restriction (ICR) and chronic caloric restriction (CCR) were studied separately by seven studies [13, 15, 17, 24, 27, 32, 51]. The period of restriction ranged from one week to three weeks in ICR, followed by an equal time of feeding at AL. Six of the seven studies concluded clearly that ICR was more

### Table 2. Animal experiments of carbohydrate restriction/ketogenic diet and cancer.

| Author(Year) | Model | Tumor |
|--------------|-------|-------|
| Zhou 2007    | Mice  | Brain, TP | High-C; KC, KC-R(KC-restricted) |
| Staffor 2010 | Mice  | Brain, TP | SD; KD |
| Abdelwahab 2012 | Mice | Brain, TP | SD; KC; SD+Radiation; KC+Radiation |
| Freedland 2008 | Mice | Prostate, TP | NCKD; low-fat; Western diet |
| Mavropoulos 2009 | Mice | Prostate, TP | NCKD; low fat/high-C(LFD); high-fat/moderate-C(MCD) |
| Wheatley 2008 | Mice | Colonic, TP | low-C; high-C(HC); HC restricted; diet-induced obesity |
| Otto 2008    | Mice  | Gastric, TP | SD; KD |
| Poff 2013    | Mice  | Metastatic, TP | SD; KD |
| Ho 2011      | Mice  | /, TP | Western diet; 8%; C; 15%; C; 10%C |

- **C**<sup>b</sup>: Conclusion of the study, “+” indicates a positive conclusion and “-” represents a negative conclusion; **Q**: Quality of the study according to a critical checklist of the Stroke Therapy Academic Industry Roundtable; **S**: The step(s) of cancer that dietary restriction regimens interfere during the initiation, progression and metastasis of cancer, “I” indicates initiation, “P” indicates progression and “M” indicates metastasis; **TP**: transplanted; C: carbohydrate; KC: a nutritionally balanced and commercially available ketogenic diet; SD: standard diet; KD: ketogenic diet; not specified; NCKD: no-carbohydrate ketogenic diet.

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**Table Footnotes:**

*aTime: Time of study (weeks); bC: Conclusion of the study, “+” indicates a positive conclusion and “-” represents a negative conclusion; cQ: Quality of the study according to a critical checklist of the Stroke Therapy Academic Industry Roundtable; dS: The step(s) of cancer that dietary restriction regimens interfere during the initiation, progression and metastasis of cancer, “I” indicates initiation, “P” indicates progression and “M” indicates metastasis; eTP: transplanted; fC: carbohydrate; gKC: a nutritionally balanced and commercially available ketogenic diet; hSD: standard diet; iKD: ketogenic diet; j: not specified; kNCKD: no-carbohydrate ketogenic diet.*

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effective in tumor prevention than CCR, while the remaining study did not specify (data not shown).

Moreover, one study showed that late-onset CR which means applying CR diet after a period of AL diet also retarded epithelial lesion development.

**KD**

Nine studies explored the relationship between carbohydrate restriction and cancer [56–64] (Table 2). All studies used the murine models. The studied tumors included prostate, brain, colonic, gastric and metastatic cancers. Transplanted models were applied by all the involved studies. Eight of the nine studies (88.9%) supported that carbohydrate restriction is protective on cancer. One study using the mouse model and colon cancer showed that low carbohydrate diet could not slow down tumor growth. Eight articles investigated the role of KD on progression of cancer, and seven of them held a positive conclusion. One article researched the role of KD on metastasis of cancer and indicated the role is efficient. Weight changes were not uniform among the involved studies. The

### Table 3. Animal experiments of intermittent fasting and cancer.

| Author(Year) | Model | Tumor | Feeding Regimens | Sample size | Time<sup>a</sup> | Body weights(g) | Major Results | C<sup>b</sup> | Q<sup>c</sup> | S<sup>d</sup> |
|--------------|-------|-------|------------------|-------------|----------------|-----------------|---------------|-------|-------|-------|
| BuschemeyerIll 2010 | Mice | Prostate, TP<sup>e</sup> | AL; 1D fasted 6D AL<sup>h</sup>; 1D fasted 5D paired feeding; 14% CR<sup>i</sup>; 2D fasted 5D AL; 28% CR | 15/group | >5 | Reduced body weights in the latter two groups | Tumor volume and survival: no significant differences. | - | 4 | P |
| Thomas II 2010 | Mice | Prostate, TP | AL: IF (twice-weekly 24 h fasts) | 50:50 | >4 | No significant difference | IF didn’t delay tumor growth | - | 4 | P |
| Tomasi 1999 | Rats | Hepatic, C | Control; IF (3D followed by 11D refeeding) | 11:11 | 48 | 371; 368 | Tumor incidence: 36%; 72% | - | 4 | I |
| Rocha 2002 | Rat | Hepatic, C<sup>i</sup> | AL; IF (48 h weekly fasting) | 12:12 | 52 | 355.2; 445.8 | Number; size of liver nodules: IF<AL | + | 4 | I |
| Saleh2013 | Mice | Mammary, TP | IF(alternate day feewing); 30%CR; AL | 80(total) | 6 | Reduced weight in CR | Tumor growth delay of ADF and CR | + | 4 | P |
| Lee 2012 | Mice | Multiple, TP | Control, two cycles of fasting (48 h each) | 41(total) | >6 | Regain weight when refeding | Fasting retard tumor growth | + | 3 | P |
| Marsh 2008 | Mice | Brain, TP | Late-onset intermittent CR feeding; AL | 7.8 | >20 | Reduced in intermittent feeding | Tumor weight: IF<AL | + | 3 | P |
| Berrigan 2002 | Mice | /, TG<sup>j</sup> | AL; 40%CR; IF(1day/week) | 31-32/group | >48 | CR<Fast<AL | Tumor free survival: CR->AL; Fast>AL | + | 4 | I |

<sup>a</sup>Time: Time of study (weeks); <sup>b</sup>C: Conclusion of the study, “+” indicates a positive conclusion and “-” represents a negative conclusion; <sup>c</sup>Q: Quality of the study according to a critical checklist of the Stroke Therapy Academic Industry Roundtable; <sup>d</sup>S: The step(s) of cancer that dietary restriction regimens interfere during the initiation, progression and metastasis of cancer, “I” indicates initiation, “P” indicates progression and “M” indicates metastasis; <sup>e</sup>TP: transplanted; <sup>f</sup>D: Day; <sup>g</sup>AL: Ad libitum; <sup>h</sup>CR: caloric restriction; <sup>i</sup>C: Chemical-induced; <sup>j</sup>TG: transgenic.

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composition of carbohydrate in the studies ranged from 0 to 20%. The major results were presented as tumor growth and tumor volume. A nutritionally complete and commercially available ketogenic diet was studied, and the two relevant studies all got positive conclusions although one was based on restricted amounts.

IF
There are eight studies about IF and cancer \[33, 42, 65–70\] (Table 3). The fasting time ranged from 24 to 72 hours. The murine models were used. The most studied tumor types were prostate and hepatic cancers. Transplanted model, chemical-induced model and transgenic model were applied. Five of the eight studies (62.5%) got positive conclusion, two of them used fasting cycle (48 h) with no specified intermittent time and late-onset intermittent fasting. Three studies investigated the role of IF on initiation of cancer, and two of them showed the efficient role of IF. Five studies searched the role of IF on progression of cancer, and three of them supported the positive conclusion. Two studies analyzed both IF and CR, and IF was functional in delaying tumor growth although the effect was not obvious as CR. Three studies obtained a negative conclusion that IF was not significantly protective on cancer. The weight changes were not uniform among the involved studies.

Meta-analysis
Tumor incidence was the most frequently used outcome with specific data (in 22 studies). Twenty-one of them were about CR. The raw data of each study with tumor incidence were pooled in our study (Fig. 2). The random-effect model was applied as heterogeneity existed (I^2=75.5%, p<0.01). The pooled OR (95%CI) for CR was 0.20 (0.12, 0.34) relative to the controls, and this indicated that CR plays a preventive role against cancer.

Discussion
In this study, we reviewed the 59 animal experimental studies on dietary restriction regimens and analyzed the data to study roles of caloric restriction, ketogenic diet and intermittent fasting during initiation, progression and metastasis of cancer in animal models. Our research indicates that CR is preventive on cancers as about 91% of relevant studies support the conclusion and the result of meta-analysis is significant. Our findings also indicate that KD can prevent cancer although there are no convincing pooled data. However, no enough evidence indicates the preventive effect of IF on cancers.

A meta-analysis on CR and spontaneous breast cancers in mice between 1942 and 1994 \[71\] found that energy-restricted animals developed 55% less breast cancers than the controls, which was similar to our findings focused on studies between 1994 and 2014.
Though CR was strongly associated with reduced cancer risk in animal models, the effect in human is still unknown. It is almost impossible to assess the long-term cancer incidence of healthy people with CR diet. The existing clinical trials were most conducted in obese cancer patients, with biomarkers as the most detected index. However, conclusions of these clinical trials were not always the same. In a study investigating the effect of dietary intervention, the newly-diagnosed obese prostate cancer patients were randomized to a CR diet group or a control group and differences in weight loss and insulin-like growth factor (IGF)-binding protein-3 (IGFBP-3) levels were found in the CR group [72]. IGFBP-3 is the most abundant IGFBP and serum level is positively associated with prostate cancer [73,74]. In a study about obese postmenopausal women, no significant changes of IGF-1 or IGFBP-3 were detected in the dietary-induced weight loss group, but the ratio of IGF-1/IGFBP-3 increased in this intervention group [75], which were inconsistent with another study [72] or with the findings from animal experiments [24,27]. In a randomized controlled trial, the levels of inflammation biomarkers were reduced in postmenopausal women with a CR weight loss diet [76], and this result was meaningful as increased levels of inflammatory
Biomarkers are associated with increased risk for some cancers [77–79]. Gene expression in breast tissue was also studied in obese women, as well as abdominal tissues, and significant changes were detected in glycolytic and lipid synthesis pathways following CR [80]. And gene included like Stearoyl-CoA desaturase (SCD) was found to be a key factor in regulation of tumorigenesis in vivo [81].

The included animal experiments indicate that ICR is more effective than CCR in prevention of cancers. A clinical trial [82] comparing ICR (2 days/week) and CCR in young overweight women showed that both ICR and CCR involved a 25% energy restriction. Except that ICR was equally effective for weight loss as CCR, the changes of many markers detected like CPR, IGF-1, IGFBP-1, and IGPBP-2 were also similar between the two groups. The study obtained a conclusion that ICR may be an equivalent alternative to CCR for weight loss and reducing disease risk.

KD may also have great potential in cancer prevention in our study, which was supported by eight of the nine included studies. The relationship between KD and cancer is unclear in the clinical realm. One study [83] comparing the effect of intermittent energy and carbohydrate restriction (<40 g carbohydrate/d for 2 d/week) with daily energy restriction in overweight women showed that the former is superior to the latter in improvement of insulin sensitivity and reduced body fat. However, this study was not directly related to KD. Nebeling et al [84] tried to assess the effects of ketogenic diet in two patients with advanced malignant astrocytoma tumors, the result that glucose uptake at the tumor site was reduced. Several existing clinical trials detecting KD in the oncology population are still ongoing [6].

IF may not be an ideal dietary intervention in animal experiments since 37.5% of the included studies provided negative results. However, the results of clinical experiments are unclear. A case series report [85] showed that fasting combined with chemotherapy is safe and may weaken the chemotherapy-induced side effects although only 10 cases were included. In the research, patients voluntarily fasted for up to 180 hours before and/or following chemotherapy [85]. Fasting cycles combined with chemotherapy drugs were also studied in animal experiments [66], and were effective and could prolong cancer-free survival. However, clinical data for IF are sparse, and some other existing clinical trials assessing IF in the oncology population are still ongoing [6].

However, human experience for applying these dietary restriction regimens in cancer prevention is limited. There are many shortcomings in the existing clinical experiments. Firstly, many studies lack control groups and reliabilities of these studies are not enough. Secondly, the restriction regimens cannot always be tolerated by all the subjects through the study. Thirdly, the research periods are short, and the long-term effects of dietary regimens cannot be well explained. Fourthly, the results are often shown as changes of biomarkers instead of direct evidence.

Moreover, there are several obstacles on the way to use these dietary restriction regimens as a treatment or preventive intervention for cancer. For example, some dietary intervention methods are unadherable in the long run. Many side effects
can be caused [6]. However, researchers are trying to solve the challenges so as to adopt these dietary habits into humans. For example, an effective promoted way is CR mimetics, which can also play an anticancer role like CR but without requiring drastic energy restriction [86]. IGF-1 and Akt/mTOR pathways are potential important mediators in the anticancer function of CR, and pharmacologic interventions targeted at these pathways are of great value. A variety of agents will affect the pathways [87]. Some agents targeting at IGF-1 receptor like monoclonal antibodies and small-molecule tyrosine kinase inhibitors are under clinical trials for many cancers [88].

Prospectively, the role of dietary restriction regimens against cancers in animal models has been studied extensively, but the achievements have not been verified in humans. Therefore, more clinical experiments are needed. Regarding the difficulty in applying these dietary restrictions into humans, more tolerable regimens should be developed. Since conditions differ among cancer patients, individualized treatment plan is necessary, so that each patient can achieve the best therapeutic effect. The incidence of malnutrition is high in cancer patients, and some patients even suffer from cachexia. Consequently, dietary restriction therapy might be a problem for these patients as nutritional support is necessary. There should be a balance between dietary restriction and nutritional support. Efforts should be made to thoroughly investigate the mechanism of dietary regimens acting on tumors, and develop agents interfering with the pathways. Mimetics which can replace dietary modifications is a progressing potential area.

In this study, we reviewed animal experimental data of three dietary restriction regimens (CR, IF and KD) and pooled the accessible tumor incidence data of CR. This study has some limitations. First, only experiments since 1994 were collected, which may affect our conclusions because there are also some valuable studies before. Second, heterogeneity existed when pooling the data of CR, probably due to the differences in animal models, cancer types, sample size, or observation time. Third, other data such as tumor volume and survival time were not pooled due to the small number of relevant studies. Fourth, there are few clinical experiments, thus only animal experiments were systematically analyzed.

In conclusion, the research indicates that CR and KD are effective in prevention of cancers in animal experiments, but the role of IF is doubtful. More clinical trials are needed to investigate the effectiveness and safety of these dietary regimens. Dietary restriction regimen which is more suitable in human for cancer prevention and therapy should be detected. And the valuable but more tolerable ways that can replace dietary restriction should be further explored.

Supporting Information

S1 Checklist. PRISMA Checklist of this meta-analysis.
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Author Contributions

Conceived and designed the experiments: MML XYZ. Performed the experiments: MML XYZ HW FW WXG. Analyzed the data: MML XYZ. Contributed reagents/materials/analysis tools: HW FW. Wrote the paper: MML XYZ.

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