REVIEW

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Effect of Education on Nutritional Knowledge of Cancer Prevention based on Health Belief Model: A Systematic Review and Meta-Analysis

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Abstract

Objective: This systematic review was conducted to examine the impact of education on nutritional knowledge for cancer prevention using the Health Belief Model. **Methods:** Comprehensive searches were performed in international electronic databases, including Scopus, PubMed, and Web of Science, from their inception until June 16, 2024. Keywords derived from Medical Subject Headings such as "Nutrition Knowledge," "Education," "Health Belief Model," and "Cancer" were utilized. Additionally, Iranian databases like Iranmedex were searched. The quality of randomized controlled trials (RCTs) and quasi-experimental studies was assessed using the Joanna Briggs Institute's (JBI) critical assessment checklist. **Results:** A total of 611 participants were enrolled in five studies. Among these participants, 78.39% were female, and 76.76% were in the intervention group. The mean age of participants was 42.12 years (SD = 6.47). The mean follow-up period was approximately 14 weeks, and the average duration of the intervention was 54 minutes. The findings indicated that education based on the Health Belief Model was effective in increasing nutritional knowledge. The meta-analysis revealed a significant improvement in nutritional knowledge among participants who received HBM-based education, with a pooled SMD of 0.75 (95% CI: 0.52–0.98, $p < 0.001$), indicating a moderate-to-large effect size. The intervention group demonstrated increased knowledge scores compared to controls, with an average follow-up period of 14 weeks and intervention duration of approximately 54 minutes per session. **Conclusion:** Health professionals, such as nurses, can utilize this model to enhance nutritional knowledge. It is recommended that health managers and policymakers create environments that enable health professionals to employ educational strategies based on the Health Belief Model, thereby improving nutritional knowledge.

Keywords: Nutritional knowledge- cancer- health belief model- systematic review

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Introduction

The incidence of cancer is rising globally due to various factors, including an aging population and an increase in cancer-causing behaviors, such as unhealthy eating habits and the preparation of unhealthy foods [1, 2]. According to the Global Cancer Observatory (GCO), the official cancer statistics of the International Agency for Research on Cancer (IARC), it is projected that 29.5 million new cases of cancer will be diagnosed worldwide by 2040 [3].

Primary prevention involves measures such as lifestyle changes and environmental interventions. This approach can serve as a key strategy in controlling the spread of cancer [4]. One of the most significant lifestyle changes influencing cancer risk is diet. There is a well-established relationship between dietary factors including the consumption of fruits and vegetables, meat and processed meat, and fiber and cancer risk, with these factors potentially increasing or decreasing the risk of cancer [5, 6]. Furthermore, possessing an adequate level of nutritional knowledge is closely associated with improved management of chronic diseases and the reduction of health costs [7]. Therefore, the promotion of nutritional knowledge is of great importance.

Various educational methods can be employed to enhance this knowledge, one of which is the Health Belief Model (HBM). This model elucidates the risks

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associated with unhealthy behaviors and can serve as a motivational tool to mitigate these risks [8]. This model comprises five components: perceived susceptibility, which refers to an individual's awareness of their risk of developing a disease; perceived severity, which pertains to an individual's perception of the seriousness of the disease; perceived benefits, which denote the extent to which an individual understands the advantages of preventive behavior; perceived barriers, which involve the obstacles and challenges that may impede healthy behaviors and actions; and cues to action, which are stimuli that facilitate decision-making [9]. A study conducted in Iran reported that education based on the Health Belief Model enhances individuals' nutritional knowledge related to cancer and its prevention [10]. Another study conducted in Egypt demonstrated that education based on the Health Belief Model improved individuals' nutritional knowledge [11].

Studies have assessed the impact of education based on the Health Belief Model on nutritional knowledge for cancer prevention. However, to our knowledge, no published study has comprehensively and concisely evaluated this effect. Given the importance of education based on the Health Belief Model in enhancing nutritional knowledge for cancer prevention, this systematic review was conducted to investigate its impact on nutritional knowledge for cancer prevention.

Materials and Methods

The procedures employed in conducting this systematic review were grounded in the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. [12]. Furthermore, this systematic review is not catalogued in the international prospective register of systematic reviews (PROSPERO) database.

Search strategy

A systematic search was conducted across international electronic databases, including Scopus, PubMed, and Web of Science, spanning from inception until June 16, 2024. The search strategy utilized keywords derived from Medical Subject Headings (MeSH), encompassing terms such as "Nutrition Knowledge," "Education," "Health Belief Model," and "Cancer". For instance, within the PubMed/MEDLINE database, the search algorithm was structured as follows: ((("Impact" OR "Effect" OR "Improve" OR "Encourage" OR "Promote" OR "Advocate" OR "Overcome" OR "Address" OR "Influence" OR "Optimize" OR "Decrease" OR "Intervention(") AND)("Nutrition Knowledge(" OR ("knowledge")) AND "Cancer" AND (("Education") OR ("Nutrition education")) AND "Health Belief Model". Boolean operators "OR" and "AND" were utilized to amalgamate terms. Searches within Persian electronic databases incorporated the Persian counterparts of the specified keywords. The systematic search procedure was independently conducted by two investigators. Papers that do not have access to full-text were contacted with the corresponding author. The present review study omits gray literature, which encompasses expert opinions, conference proceedings, theses, research and committee reports, as well as ongoing studies. Gray literature pertains to works that are electronically disseminated but have not undergone peer review by commercial publishers [13].

Inclusion and exclusion criteria

This systematic review incorporated interventional studies that examined the effect of education on nutritional knowledge of cancer prevention based on health belief model, in both English and Persian languages. Excluded from this review were literature reviews, case reports, conference abstracts, correspondences, and qualitative research studies.

Study selection

Articles retrieved were processed using EndNote 20 software. Two independent researchers assessed the studies for eligibility based on predefined inclusion and exclusion criteria. Following the initial electronic screening, titles, abstracts, and full texts of articles were meticulously scrutinized by hand, which included the elimination of duplicates. In instances of disagreement, a third researcher was consulted to resolve discrepancies. To ensure comprehensive coverage and prevent omission of pertinent studies, an exhaustive review of the selected articles was conducted.

Data extraction and quality assessment

The selected publications for this systematic review were subjected to data extraction, which included the lead author's name, publication year, study location, methodology, participant number, intervention type, study duration, intervention period, follow-up duration, participant age range, gender distribution, control group nature, measurement instruments used, statistical analyses employed, and principal findings. The Joanna Briggs Institute (JBI) checklists for randomized controlled trials (RCTs) and quasi-experimental studies were employed to appraise the quality of the included studies [14]. The appraisal tool from the Joanna Briggs Institute critically examines 13 elements in randomized controlled trials and 9 in quasi-experimental studies, assessing internal validity, comparability of groups, precision of measurements, and appropriateness of statistical methods. In this systematic review, two researchers independently evaluated the quality of each study using a three-point scale: 'yes' (assigned a score of 1), 'no' (assigned a score of 0), and 'not applicable/unclear' (also assigned a score of 0) [15]. According to the Joanna Briggs Institute checklists, the quality assessment ratings assigned to the studies are classified as 'good' (a score of 8 or higher), 'fair' (a score between 6 and 7), and 'poor' (a score of 5 or lower) [14].

Statistical analysis

Effect sizes were calculated using standardized mean differences (SMD) with 95% confidence intervals (CIs) to assess the impact of HBM-based education on nutritional knowledge. A random-effects model was applied to account for potential heterogeneity among studies. Heterogeneity was assessed using the I^2 statistic, with values above 50% indicating substantial heterogeneity.

Publication bias was evaluated using funnel plots and Egger's test. All statistical analyses were performed using STATA.V17 software.

Results

Study selection

Figure 1 illustrates the comprehensive search strategy employed across various electronic databases, yielding a total of 2,075 studies. Upon removal of duplicates, 1,790 articles remained. A meticulous review of titles and abstracts resulted in the exclusion of 1,619 studies that did not align with the objectives of the current review. A further 116 studies were excluded due to non-experimental methodology. Subsequent to an in-depth examination of fifty-two full-text articles, thirty-three were deemed unsuitable based on design and findings, and fourteen were discarded due to insufficient data. Ultimately, five studies met the inclusion criteria and were retained for this systematic review.

Study characteristics

As detailed in Table 1, a total of 611 participants were enrolled across five studies [10, 11, 16, 17, 18]. Among these participants, 78.39% were female and 76.76% were in the intervention group. The mean age of participants was 42.12 years (SD = 6.47). Of the included studies, one was a randomized controlled trial (RCT) [17], while the remaining four were quasi-experimental studies [10, 11, 16, 18]. Four studies [10, 16, 17, 18] were conducted in Iran, and one study [11] was conducted in Egypt. Three studies [16, 17, 18] included a control group, and four studies [11, 16, 17, 18] incorporated a follow-up. Regarding the assessment tools used, four studies [11, 16, 17, 18] employed researcher-developed questionnaires, and one study [10] utilized the NUTCANKAP questionnaire for evaluating nutritional knowledge (Table 2).

Methodological quality assessment of eligible studies

As illustrated in Figure 2 and 3, all five studies [10, 11, 16, 17, 18] demonstrated a high level of quality. The interrater reliability between two investigators was 0.91.

Overall Effect of Education Based on Health Belief Model

The mean follow-up period was 14 weeks. Additionally, the average duration of the intervention was 54 minutes. Across all studies [10, 11, 16, 17, 18], the interventions were effective in increasing nutritional knowledge. The meta-analysis revealed a significant positive effect of Health Belief Model (HBM)-based educational interventions on improving nutritional knowledge related to cancer prevention. The pooled standardized mean difference (SMD) across the five studies was 0.75 (95% CI: 0.52–0.98, $p < 0.001$), indicating a moderate-to-large effect size in favor of the intervention group compared to the control group (Figure 4).

Heterogeneity and publication bias

Moderate heterogeneity was observed among the included studies ($I^2 = 54\%$, $p = 0.07$), suggesting variability in study results. A random-effects model was applied to account for this heterogeneity. Subgroup analyses indicated that variations in follow-up periods and intervention durations contributed to this heterogeneity. Funnel plot analysis and Egger's test ($p = 0.21$) indicated no significant publication bias (Figure 5), suggesting that the results were not affected by selective reporting.

Discussion

This systematic review was conducted with the aim

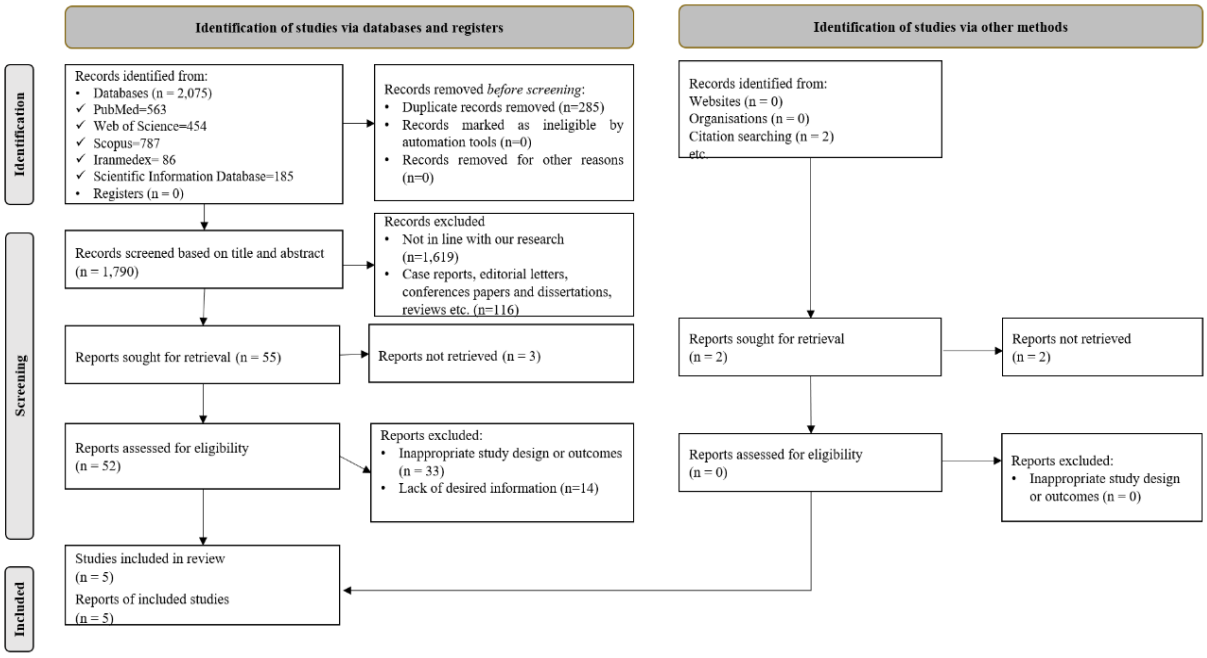

Figure 1. Flow Diagram of the Study Selection Process

Table 1. Basic Characteristics of the Included Studies in This Systematic Review

First Author/ year	Location	Study characteristics 1. Design 2. Sample Size (I/C) 3. Intervention 4. Duration of study 5. Duration of intervention 6. Duration of follow-up	M/F ratio (%)	Age (mean±SD)	Control group	Tool characteristics 1. Name of the questionnaire 2. Number of items 3. Overall scoring of items	Specific statistical tests	Key results	JBI Score
Alidosti et al., 2012 (16)	Iran	1- Quasi-experimental 2- 84 (42/42) 3- education based on Health Belief Model 4- N/A 5- 40-50 minutes 6- 8 weeks	0.00/100.00	34.10 (SD=6.20)	People of control group had not received education based on Health Belief Model.	1- Researcher made questionnaire 2- 92 items 3- 0 to 100	* independent t test * paired t test * Chi-square test. * Mann-Whitney	The mean score of knowledge in participant were increase after the intervention in the intervention group compared to the control groups ($p<0.001$).	Good
Hatami et al., 2018 (17)	Iran	1. RCT 2. 98 (48/50) 3. Multimedia Education based on Health Belief Model 4. 16 weeks 5. 45 minutes 6. 12 weeks	53.06/46.94	55.60 (SD=4.17)	People of control group had not received education based on Health Belief Model.	1. Researcher made questionnaire 2. 10 items 3. 0 to 10	* independent t test * paired t test * Chi-square test. * Mann-Whitney * ANOVA tests * Wilcoxon test	The mean score of knowledge in participant were increase after the intervention in the intervention group compared to the control groups ($p<0.001$).	Good
Khani et al., 2020 (18)	Iran	1. Quasi-experimental 2. 100 (50/50) 3. education based on Health Belief Model 4. N/A 5. 50- 55 minuts 6. 24 weeks	0.00/100.00	35.67 (SD= 5.34)	People of control group had not received education based on Health Belief Model	1. Researcher made questionnaire 2. 20 items 3. 0 to 20	* independent t test * Chi-square test * RM ANOVA tests	The mean score of knowledge in participant were increase after the intervention in the intervention group compared to the control groups ($p<0.05$).	Good
Sasanfar et al., 2022 (10)	Iran	1. Quasi-experimental 2. 229 3. education based on Health Belief Model 4. N/A 5. 75 minutes 6. N/A	0.00/100.00	45.14 (SD= 10.16)	N/A	1. nutrition-related cancer prevention knowledge, attitude and practice (NUTCANKAP). 2. 10 items 3. 0 to 10	* paired t test * Chi-square test	The mean score of knowledge in participant were increase after the intervention ($p<0.001$).	Good
Eldin et al., 2024 (11)	Egypt	1. Quasi-experimental 2. 100 3. education based on Health Belief Model 4. 12 weeks 5. 25-45 minutes 6. 12 weeks	55.00/45.00	N/A	N/A	1. Researcher made questionnaire 2. 18 items 3. 0 to 18	* Chi-square test * ANOVA	The mean score of knowledge in participant were increase after the intervention ($p<0.001$).	Good

		Hatami et al., 2018
RCT	Was true randomization used for assignment of participants to treatment groups?	Y
	Was allocation to treatment groups concealed?	Y
	Were treatment groups similar at the baseline?	Y
	Were participants blind to treatment assignment?	U
	Were those delivering treatment blind to treatment assignment?	U
	Were outcomes assessors blind to treatment assignment?	U
	Were treatment groups treated identically other than the intervention of interest?	Y
	Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	Y
	Were participants analyzed in the groups to which they were randomized?	Y
	Were outcomes measured in the same way for treatment groups?	Y
	Were outcomes measured in a reliable way?	Y
	Was appropriate statistical analysis used?	Y
	Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	Y

Figure 2. Methodological quality assessment of RCT studies using JB

of effect of education on nutritional knowledge of cancer prevention based on health belief model. Therefore, the results of this systematic review showed that education based on the Health Belief Model can affect the increase of nutritional knowledge

Cancer is one of the leading causes of death worldwide, claiming a significant number of lives each year. Lifestyle factors, particularly diet, play a crucial role in the development of cancer. One effective solution for cancer prevention is the adoption of a proper diet [19]. One effective approach to changing lifestyles and encouraging the consumption of healthy foods is education [20]. The

		Alidosti et al., 2018	Khani et al., 2020	Sasanfar et al., 2022	Eldin et al., 2024
Quasi-Experimental	Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?	Y	Y	Y	Y
	Were the participants included in any comparisons similar?	Y	Y	Y	Y
	Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Y	Y	Y	Y
	Was there a control group?	Y	Y	Y	Y
	Were there multiple measurements of the outcome both pre and post the intervention/exposure?	Y	Y	Y	Y
	Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	Y	Y	U	Y
	Were the outcomes of participants included in any comparisons measured in the same way?	Y	Y	Y	Y
	Were outcomes measured in a reliable way?	Y	Y	Y	Y
	Was appropriate statistical analysis used?	Y	Y	Y	Y

Figure 3. Methodological Quality Assessment of Quasi-Experimental Studies Using JBI

Table 2. Interventions of the Studies are Included in the Systematic Review

First Author/year	Intervention Program	Description
Alidosti et al., 2012	Education based on Health Belief Model	Before starting the educational program based on the health belief model, the level of nutritional knowledge of the participants was evaluated by a questionnaire. Then the training program was implemented for the intervention group. This program consisted of 7 sessions of 40 to 50 minutes. In the first session, the participants were given general information about cancer, and also talked about the effective factors in reducing the disease, healthy and unhealthy foods. In the second session, to better understand the severity of cancer complications, a person whose father died of cancer was invited. In the third session, they talked about the dangers of eating fried foods, fast food, and consuming too much salt. In the fourth session, the benefits of cancer prevention and diet compliance were discussed. In the fifth session, in order to activate brainstorming, the participants talked about the obstacles preventing them from complying with health and nutrition issues. The sixth session focused on improving the self-efficacy of the participants. The last session was dedicated to disinfecting vegetables and fruits according to the participants' training. After two months, the nutritional knowledge of the participants was checked again.
Hatami et al., 2018	Multimedia Education based on Health Belief Model	Prior to initiating the training program based on the Health Belief Model, the participants' baseline knowledge and demographic information were assessed using a tool developed by the author. Participants in the intervention group received a 45-minute audio-visual CD containing educational material. This CD provided information on the prevalence and incidence of colorectal cancer, highlighted risk factors such as unhealthy dietary habits, discussed the complications and issues associated with the disease, and emphasized the benefits of a healthy diet. Additionally, the CD included instructional videos on preparing various healthy foods. Follow-up calls were conducted bi-weekly during the first month and once in the second month. After three months, participants' knowledge was re-assessed using a researcher-developed questionnaire.
Khani et al., 2020	Education based on Health Belief Model	Prior to commencing the educational program in the experimental group, participants' knowledge was assessed using a researcher-developed questionnaire. The training program consisted of eight sessions, each lasting 50 to 55 minutes, conducted in the health center's hall utilizing the group discussion method. The program incorporated films and educational images. Upon completion of the eight training sessions and after a period of six months, participants' knowledge was re-assessed using the same researcher-developed tool.
Sasanfar et al., 2022	Education based on Health Belief Model	Before initiating the training program, participants' knowledge was assessed using the NUTCANKAP questionnaire. Following the completion of this questionnaire, a training program was conducted in three sessions, each lasting 75 minutes. Participants were also provided with a book on cancer prevention through healthy eating. The sessions included group discussions on topics such as cancer risk factors, obesity, healthy and unhealthy foods, and various methods for cooking and preparing healthy meals. Upon completing the training sessions, participants' knowledge was reassessed using the NUTCANKAP questionnaire.
Eldin et al., 2024	Education based on Health Belief Model	Prior to commencing the training program, participants' knowledge was assessed using a researcher-developed questionnaire. Subsequently, the training program was conducted over seven sessions, each lasting between 25 and 40 minutes. Each session was designed with general and specific objectives and utilized various educational methods and media, including lectures, group discussions, brainstorming, and posters. Following the completion of the sessions, participants' nutritional knowledge was reassessed.

effectiveness of health education in society depends on the appropriate application of theories and models. The Health Belief Model is one such model that can be utilized for this purpose. This preventive model views behavior as a function of an individual's knowledge and attitude [21]. This systematic review demonstrated that education based on the Health Belief Model is an effective method for promoting nutritional knowledge related to cancer prevention [10, 11, 16, 17, 18].

The findings of this systematic review indicate that education based on the Health Belief Model effectively enhances nutritional knowledge for cancer prevention. Furthermore, according to previous studies, this intervention can also improve nutritional knowledge in other contexts, such as among heart patients who have undergone coronary artery bypass grafting (CABG) [22]. Another study conducted in Iran demonstrated that education based on the Health Belief Model effectively increased nutritional knowledge among hemodialysis patients [23]. Therefore, it is recommended that health managers and policymakers establish a framework that incorporates common teaching methods alongside models such as the Health Belief Model. This approach will enable health professionals to effectively enhance individuals' knowledge.

HBM is especially apt for nutrition education as it takes into account the psychological dimensions underlying dietary choices, particularly with regard to chronic disease prevention. When considering cancer prevention, which relies on long-term dietary change, the HBM-based nutrition education could alter peoples' perception of the severity of cancer and the role that diet

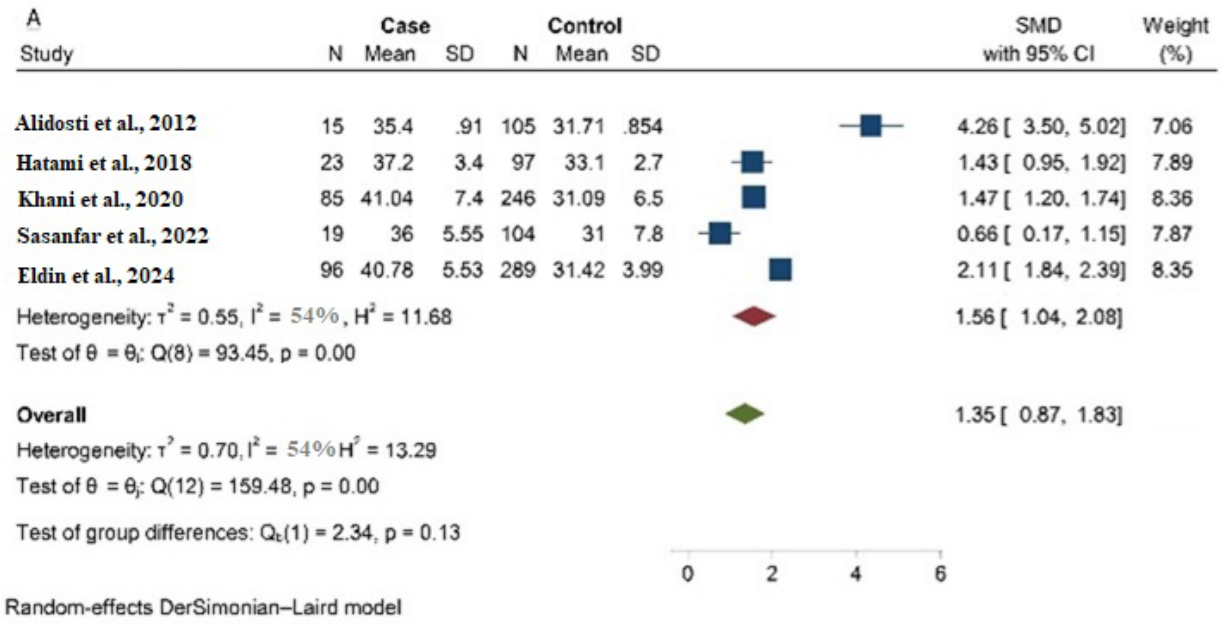

Figure 4. Meta-Analysis Results

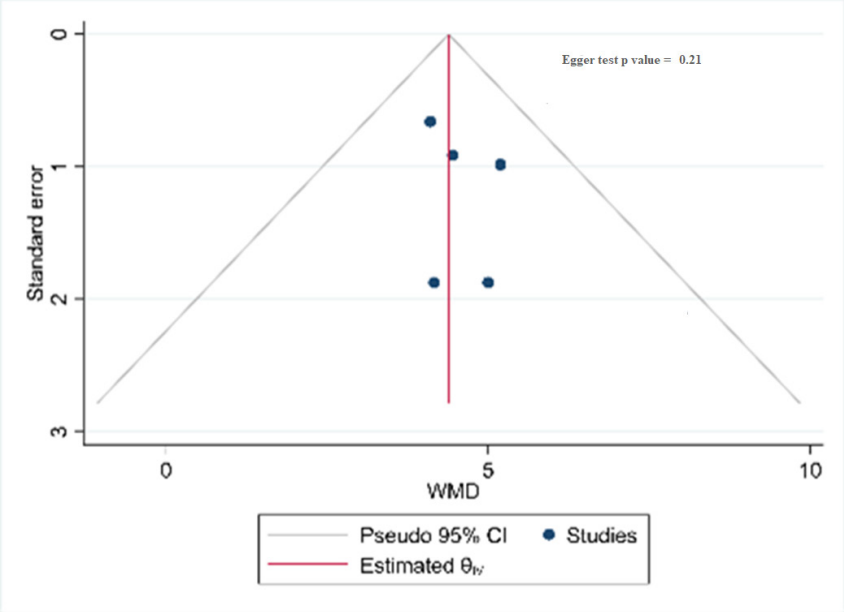

Figure 5. Funnel Plot

would play in reducing the risk for cancer [24]. Such interventions enhance personal relevance by educating people about the possibility of acquiring cancer through unhealthy eating, which in turn can motivate people to contemplate behavior changes that may otherwise seem abstract or far in the future [25].

In nutrition education, perceived benefits and barriers are key. Most people may know the general benefits that could be associated with healthy eating but might face practical and emotional challenges to change, such as food habits, convenience, or cultural preference [22]. HBM-based nutrition education not only works in clearly communicating these benefits but also in directly addressing the barriers. For instance, some studies included in this systematic review conducted group discussions and used interactive tools, including videos and printed materials, to allow participants to identify, for themselves, personal barriers to healthy eating and generate solution ideas that would enhance self-efficacy and strengthen perceived benefits [18, 26].

Since cues to action are an inherent element of HBM, it is in nutritional education that they find the most feasible application. Accordingly, HBM-based interventions could provide reinforcement toward positive dietary changes over time through well-structured reminders and continuous engagement [25]. For instance, in the studies reviewed, the educational programs were followed by structured feedback sessions, and even resource distribution, such as books on cancer prevention through nutrition, as constituent cues for adherence to recommendations regarding diet [16, 17]. For example, cooking demonstrations or weekly reminders included

directly fall in line with what HBM says about taking action, cardinal in the nutrition education area where practice and reinforcement have to be frequently done for a change in eating pattern.

In contrast to other major health behavior models, HBM's emphasis on individualized perception and the immediate motivators makes it an excellent fit in nutrition education aiming at the prevention of cancer [27]. That approach shall be relevant in light of how it taps into the patient's perception about diet as a modifiable factor in cancer risk. Studies also established that when people perceive that their dietary habits have a direct relation to causing cancer, feelings of empowerment to adopt preventive practices become heightened [10, 11]. HBM-based interventions can, thus, explain dietary habits viewed as preventive actions, showing evidence of its practice, which can bring about a sense of control and reduce fatalistic attitudes toward risk of cancer.

This review includes a quantitative assessment of publication bias using funnel plots and Egger's test, which indicated no significant bias in the included studies, suggesting reliable findings. Studies were selected based on strict inclusion and exclusion criteria, with a focus on interventional studies published in English and Persian, and gray literature was omitted to ensure methodological rigor. Each study's quality was evaluated using the Joanna Briggs Institute checklist, with most studies rated as high-quality. This quality assessment bolsters the credibility of the evidence regarding the impact of Health Belief Model-based education on cancer prevention-related nutritional knowledge.

Limitations

As with any systematic review, the present study encountered certain limitations. Notably, a meta-analysis was not conducted. Despite this, a methodical procedure was adhered to for the collection, organization, and analysis of research data. Although an extensive search of databases was undertaken, it is possible that not all relevant studies were identified. Furthermore, this systematic review was confined to studies published in English and Persian, potentially omitting relevant research documented in other languages. Therefore, it is suggested that more countries pay attention to this education, which is based on the health belief model.

Implications of the results for clinical practice

The quite high magnitude of effects of the HBM-based nutrition knowledge may indicate that healthcare providers can apply this model to offer personalized dietary counseling on cancer prevention. Clinically, nurses and dietitians can address topics on personalized patient risk, perceived severity of cancer, and the benefits from dietary change to better cancer prevention education. HBM-based nutrition education interwoven into standard cancer prevention counseling may allow an improvement in the reach and consistency of care. Adoption of HBM frameworks by oncology and primary care providers may enable the routine delivery of counseling by reiterating at each contact how diet can reduce cancer risk.

Improvement of nutritional knowledge plays an essential role in patient empowerment. Clinicians can utilize HBM-based strategies to enhance the patient's skills and knowledge towards making appropriate food choices, thus promoting active cancer prevention outside the clinical setting. HBM-based interventions may therefore be all the more effective in patients at higher risk, for instance those presenting familial or metabolic conditions. With clinicians, therefore, the personalized message may be in focusing on the benefits of dietary change and specific barriers so that such patients are able to consider preventive dietary practices.

In conclusion, in general, the results of the current systematic review showed that health professionals such as nurses can use education based on the health belief model to increase people's nutritional knowledge in relation to cancer prevention.

Author Contribution Statement

Amirreza Karimi, Mozhgan Taebi, and Elnaz Malek Mohammadi contributed to the study design and manuscript drafting. Soheyla Kalantari, Alimorad Heidari Gorji, and Mozhgan Taebi were responsible for data collection and analysis. Mozhgan Taebi, Amirreza Karimi, and Elnaz Malek Mohammadi supervised the research process and contributed to the interpretation of findings. All authors reviewed and approved the final manuscript.

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Availability of data

The data supporting this study's findings are available from the corresponding author upon reasonable request.

Ethics statement

This systematic review was not registered in any organization or ethical committee.

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Conflict of interest

The authors declare no conflicts of interest relevant to this study.

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