Prostate cancer is the third most common cancer in men globally, and the most common cancer among men in the United States. Dietary choices may play an important role in developing prostate cancer; in particular, a higher dairy product intake has been associated with an increased risk of developing prostate cancer. The overall positive association between milk consumption and the risk of prostate cancer development and prostate cancer mortality has been well documented in multiple epidemiological studies. However, there is limited literature on the association between types of milk, as classified by fat content (skim, low fat, and whole), and the risk of developing prostate cancer. When further examining current state of the literature on this topic, there is a number of epidemiologic studies assessing the relationship between prostate cancer and milk consumption. On the contrary, very few experimental studies explore this topic. Further experimental research may be necessary to examine the relationship between dairy and dairy products consumption and the increased risk of development of prostate cancer. At this time, there are no formal clinical recommendations regarding dairy products consumption for patients who are at risk of prostate cancer development or who have a history of prostate cancer. In this manuscript, we sought to systematically review the existing literature on the association between milk consumption classified by fat content, and the risk of developing prostate cancer. These findings may be useful for the clinicians who provide recommendations for the patients at risk of developing prostate cancer.

Keywords: Carcinogenesis; Diet, cariogenic; Diet, western; Prostatic neoplasms

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INTRODUCTION

Despite treatment advances, prostate cancer related mortality rates remain high in the United States. While surgical treatments may play a significant role in reducing a disease progression, prostatectomy may not significantly decrease the mortality related to a localized prostate cancer when compared to an observational approach [1]. Global cancer incidence estimates reveal that, prostate cancer has become the third most common cancer in men, and half a million new cases are being reported every year [2]. The global burden of prostate cancer is going to be 1.7 million new cases by 2030 [3]. According to the Center for Disease Control, prostate cancer is the most common cancer among men in the United States and one of the leading causes of cancer deaths among men of all races. Prostate cancer mostly occurs in the elderly people with three quarters...
of the cases occurring in men who are above 65 years of age, which is suggestive of the fact that, developed countries having a higher proportion of elderly population report a higher incidence rate of prostate cancer (~15%), compared to the developing countries [2]. Incidence rates in the developing countries are continuing to increase, while mortality rates are staying at a relatively stable level [4].

A review of prostate cancer incidence data from 42 countries suggested that there may be a correlation (r=0.711) between milk consumption and prostate cancer incidence [5]. It has been observed that total dairy product intake and calcium from the dairy products has been positively associated with the risk of developing prostate cancer and it was observed that the low fat milk intake was associated with greater risk of non-aggressive form of the disease and whole milk was associated with greater risk of fatal prostate cancer [6]. The association between the risk of developing prostate cancer and dairy products has been linked to the fact that dairy products raise the concentrations of insulin like growth factors [7]. The high fat content in the dairy products has been associated with c-peptide concentration which leads to development of aggressive form of prostate cancer [8]. Metanalysis conducted by Lu and colleagues [9] suggested that increased whole milk consumption may contribute to higher prostate cancer mortality rate (2016). Another metanalysis suggested that high intake of whole milk and low fat milk may contribute to an increased risk to develop prostate cancer [10]. A study of Swedish men suggested that there is an association between whole milk consumption and cancer progression; also, this study suggested that low-fat milk intake may reduce mortality in patients with localized prostate cancer [11]. While the data suggesting that whole milk may contribute to prostate cancer development may appear rather convincing, the effects of skim and low-fat milk are not clear.

There is an abundance of epidemiologic and ecologic studies exploring the relation between prostate cancer and milk consumption. Conversely, only a small number of experimental studies has been conducted to further explore this topic. Prostate cancer development may be affected by estrogen levels [12]. It has been suggested that drinking milk may result in increase of estrone and progesterone levels in the blood [13]. Some authors speculated that modern methods of commercial milk production result in higher level of estrogen in the milk, which in turn may result in higher rates of prostate and other cancers [14]. Estrogen is not the only compound found in the milk that may affect the development of prostate cancer. One study suggested that milk protein casein may stimulate the proliferation of prostate cancer cells [15].

There is evidence that milk may reduce the risk to develop certain other cancers. For instance, participation in school milk programs has been associated with a reduced risk for developing colorectal cancer [16]. Milk provides essential amino acids, vitamins, and calcium. It is still considered an integral part of healthy diet worldwide. Milk consumption may have certain health benefits and clinical recommendation to eliminate milk from the diet completely may not be feasible. Currently, no structured clinical recommendations exist regarding milk products consumption that may affect the risk of prostate cancer development. There were several reviews of a similar nature conducted in the past [10,17-19]. However, the reviews mentioned above did not focus specifically on milk; they had broader focus, examining the relations of prostate cancer to dietary intake in general, dairy products, or vitamin D consumption. None of the reviews above focused on examining the relationship between fat content in milk and the risk for prostate cancer. To add to that notion, we attempted to create a comprehensive systematic review including all of the current evidence on the topic published in May 2020 or prior. For that reason, we examined the existing literature to explore this topic and provide recommendations for the clinicians who deal with at risk populations.

**MATERIALS AND METHODS**

1. **Search strategy**

This systematic review was conducted according to the Preferred Reporting Items for Systematic Review and Metanalysis (PRISMA) guidelines. Literature search was performed by two independent reviewers using PubMed (1982 to May, 2020), Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 to May, 2020) (Fig. 1). The search was conducted using free text search terms ‘prostate cancer’, ‘prostate cancer risk’, ‘milk’, ‘milk consumption’, ‘dairy’, and ‘dairy consumption’. Hand searches of references of other review articles were conducted by the reviewers indepen-
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2. Screening and data abstraction

Titles and abstracts were screened independently by the two researchers. If the inclusion criteria were met, then the full article was studied. Any disagreement about the inclusion of the articles was resolved by consensus. Information on the author, year of the study, geographical location of the study, type of the study design, study participants, number of the study participants, results and associations found (if any) were collected.

3. Study selection

For selection of the articles, the articles had to be in English and full text articles from 1981 to May 2020. All studies whether they showed a significant association or no association between milk consumption and risk of prostate cancer were included. For the study of association, articles were included, if they presented estimates of risk ratios, hazard ratios, or odds ratios. Studies which mentioned the association of dietary practices were included if they comprised milk consumption. Other systematic reviews, meta-analyses, articles that studied the effects of plant-based milk products, genomic studies and the articles which had titles suggestive of dealing with subjects unrelated to the search were excluded. Authors utilised the above approach to include only the original studies that evaluate the relationship between prostate cancer and milk consumption. Included were addressing the prostate cancer risk (incidence and prevalence) in relation to milk consumption or dairy consumption in general. Selected studies were assessed for risk of bias using The Cochrane Collaboration’s tool for assessing risk of bias in randomized trials [37]. All of the studies were considered having a low risk for bias after utilising the above tool.

Authors proceeded with implementing a systematic review of the selected studies because of the heterogeneity of the data in the articles, because of the heterogeneity of the data the implementation of the meta-analysis of the selected studies would not be possible.

RESULTS

There were 20 significant studies which were included in the systematic review. Three of the studies were ecological studies. One of the ecological studies compared the prostate cancer mortality rates in 1986 from 41 countries with the macronutrient supply values for 1983. In the second ecological study, cancer incidence and mortality data from 42 countries were compared with the dietary practices akin to each country. In the third ecological study, age standardized cancer mortality rates from 71 countries were compared with the food consumption data. There were 7 prospective cohort studies and 8 case control studies. Most of the studies that were incorporated were from the United States. Most of the food questionnaires were self-administered questionnaire except the ecological studies where data on food consumption for the countries involved in the

Fig. 1. Systematic review procedure.
study were collected and in one ecological study, national consumer macronutrient supply data were collected. Most of the studies focused on the milk and its association with the risk of prostate cancer while some studies included other dairy products.

### 1. Skim milk

Park and colleagues [22] found an association be-

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<table>
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<tr>
<th>Table 1. Characteristics of the studies involved in the systematic review</th>
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<tbody>
<tr>
<td><strong>Author/study year/country</strong></td>
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<td>-----------------------------------------------</td>
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<tr>
<td>Park et al (2007) [22]/1995–2001/USA</td>
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<tr>
<td>Grant (1999) [23]/study year not mentioned/ ecological study</td>
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<tr>
<td>Ambrosini et al (2008) [27]/2001–2002/Western Australia</td>
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<tr>
<td>Park et al (2007) [20]/1993–1996/USA</td>
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<tr>
<td>Downer et al (2017) [11]/1991–2011/Sweden</td>
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<td>Bosetti et al (2004) [31]/1991–2002/Italy</td>
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### Table 1. Continued

<table>
<thead>
<tr>
<th>Author/study year/country</th>
<th>Study population/data derived from</th>
<th>Study design and size</th>
<th>Method of data collection for exposure assessment</th>
<th>Exposure (outcome association and main results)</th>
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<tr>
<td>Deneo-Pellegrini et al (2012) [26] 1996–2004/Uruguay</td>
<td>Cases were men aged 40–89 years with incident and histologically confirmed prostatic adenocarcinomas from Uruguay (4 major hospitals in Montevideo), between 1996 and 2004, and controls were patients with no history of smoking/drinking/dietary changes</td>
<td>Case-control study 326 cases and 652 controls</td>
<td>Socio-demographic variables and other risk factors questionnaire and 64-item food frequency questionnaire</td>
<td>Whole milk is positively associated with the risk of prostate cancer with an OR=2.01: 95% CI=1.42–2.82, p-trend≤0.0001</td>
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<tr>
<td>Slattery et al (1990) [28] January 1, 1984–November 15, 1985/Utah</td>
<td>Cases being white males, 45–75 years with histologically confirmed first primary prostate cancer, controls men above 65 years identified by random dialling (from four urban counties of Utah, between 1984–1985)</td>
<td>Case-control 468 identified as cases of which, 362 completed the interview 891 control subjects identified of which 685 completed interviews</td>
<td>Self-administered questionnaire about adolescent diet, adolescent years, medical and family history and adult dietary intake</td>
<td>Increased prostate cancer risk associated with consuming high saturated fat, diet which includes whole milk, in adults with an OR=1.8, as compared to a lesser risk in adolescents (OR=1.2) and no major differences in risk observed in men aged 45–67 years, 68–74 years for aggressive tumors</td>
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<tr>
<td>Ganmaa et al (2002) [5] 1988–1992/ ecological study (data collected from 42 countries)</td>
<td>The incidence and mortality rates of testicular and prostatic cancers in 42 countries were correlated with the dietary practices in these countries using the cancer rates (1988–1992)</td>
<td>Ecological data Cancer incidence data and mortality data and dietary practices from 42 countries</td>
<td>“Cancer incidence in five continents” edited by Parkin et al [2]: cancer incidence data (GLOBOCAN: data on the mortality of testicular and prostatic cancers. The consumption data for various food items: FAOSTAT [Food and Agricultural Data] dataset</td>
<td>Milk was found to be correlated with mortality of prostate cancer (Correlation coefficient, r=0.766), milk+cheese contributed significantly to mortality from prostate cancer (r=0.580)</td>
</tr>
<tr>
<td>Colli and Colli (2006) [32] ecological study (data collected from 71 countries)</td>
<td>Age adjusted cancer rates from the International Agency for Research on Cancer (2000) and food consumption data (1990–1992), provided by the Food and Agricultural Organization (FAO) of the United Nations were compared</td>
<td>Ecological study Cancer mortality and food consumption rates obtained from 71 countries</td>
<td>Age standardized cancer mortality rates for 71 countries (GLOBOCAN 2000 database and per capita food intake rates from the food consumption data provided by the FAO of the United Nations)</td>
<td>Correlation found between increased prostate cancer mortality and consumption of total animal calories, total animal fat calories, meat, animal fat, milk (R=0.57), sugar, alcoholic beverages and stimulants</td>
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<tr>
<td>Torniainen et al (2007) [21] 2001–2003/Sweden and Finland</td>
<td>Swedish Study population (Cancer Prostate in Sweden [CAPS] 1 and 2) and Finnish Study population: DNA samples from prostate cancer patients (Tampere University Hospital and the Blood Center of the Finish Red Cross, Tampere)</td>
<td>Case control study Sweden: CAPS Part 1–by 1,352 cases and 858 controls CAPS Part 2–1,524 cases and 963 controls Finland: 1,229 cases and 473 controls</td>
<td>Self-administered questionnaire</td>
<td>High intake of low-fat milk (3 or more glasses of low fat milk vs. no consumption at all) was associated with an increased risk of prostate cancer in the CAPS 1 study, and the adjusted OR was 1.8 (95% CI=1.17–2.9, p-trend=0.003) for advanced cases and 1.5 (95% CI=0.98–2.3, p-trend=0.01) for localized cases</td>
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between skim milk and risk of advanced prostate cancer. While the association was statistically significant, authors discussed that this may have occurred by chance. Other milk or dairy products consumption had no association with the increased risk for prostate cancer in this study [22]. A study by Grant [23] suggested that...
consumption of skim milk and non-fat portion of milk may have high association with prostate cancer incidence. In contrast to these findings other studies examining the association between skim milk consumption and risk for prostate cancer did not suggest such an association [24,25].

2. Whole milk/high-fat milk

In one study men diagnosed with localized prostate cancer, high fat milk consumption was associated with increased prostate cancer-specific mortality while in men with advanced prostate cancer this association was not observed [11]. Whole milk was seen to be positively associated with prostate cancer risk in one study [26]. Increased odds of prostate cancer with whole milk consumption were suggested in a study [25]. A case control study was conducted in Australia to investigate the dietary patterns associated with prostate cancer risk, it was observed that the western pattern diet, which includes high-fat milk was associated with increased odds of prostate cancer risk [27].

In another study the subjects were categorized into adolescents, young adults and older adults in an attempt to study the food consumption trends and the subsequent prostate cancer risk in different groups. It was observed that there was an increased prostate cancer risk in adolescents consuming fatty foods (includes whole milk), while no significant risk was observed in adults and males aged 45–74 for aggressive tumors [28]. The odds of prostate cancer risk were 1.5 times in men who consumed whole milk as compared to men who consumed 2% milk or skim milk [29]. Contrary to those findings, a study conducted in Australia suggested that dairy and milk consumption may have an inverse association with the development of advanced prostate cancer [30].

Table 1. Continued 3

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<th>Author/study year/country</th>
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<tr>
<td>Pal et al (2019) [30]</td>
<td>Cases were men below 75 years, diagnosed with advanced prostate cancer from the Victorian Cancer Registry and controls were men below 75 years with prostate specific antigen levels above age specific limits and prostate cancer excluded by biopsy</td>
<td>Case control study 1,254 cases and 818 controls</td>
<td>Food frequency questionnaire</td>
<td>Weak inverse association observed for overall milk intake (highest vs. lowest OR=0.72, 95% CI=0.54–0.98, p-trend=0.058 (model adjusted for covariates like age, socioeconomic status, but unadjusted for trouser size)</td>
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<td>Nilsson et al (2020) [36]</td>
<td>The study is derived from the Northern Sweden Diet Database (NSDD). First sampling event in NSDD (January 1, 1986 to December 31, 2016) was chosen for this study</td>
<td>Prospective cohort study 105,891 subjects</td>
<td>Food frequency questionnaire: two versions (84 items, 64–66 items)</td>
<td>Consumption of fermented milk associated with increased prostate cancer risk compared to subjects in lowest quintile vs. highest quintile with HR Q5 (highest quintile)–Q1 (lowest quintile)=1.16, 95% CI=1.02–1.32</td>
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<tr>
<td>Steck et al (2018) [29]</td>
<td>This study used data from Prostate Cancer Project Study participants were men aged 40–79 years, Louisiana and North Carolina residents with a histologically confirmed adenocarcinoma of the prostate</td>
<td>Case only study 2,060 participants</td>
<td>Diet history questionnaire</td>
<td>Men who reported higher consumption of whole-fat milk (≥1.23 servings/d) had an increased odds of aggressive prostate cancer (OR=1.74; 95% CI=1.16–2.62), as compared to non-whole-fat milk drinkers (fully adjusted model), attenuated association seen, after adjusting for other dietary variables. No association observed with dairy product intake</td>
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*Western pattern score: high intake of red processed meats, fried fish, hamburgers, chips, high-fat milk, and white bread.*
3. Milk (skim or whole milk)
There were some other studies conducted in which the effect of milk on the risk of developing prostate cancer, rather than the skim or whole milk was investigated. In one study by Bosetti and colleagues [31] the researchers observed an increased prostate cancer risk with frequent consumption of milk and dairy products. In an ecological study examining the association between world dietary practices and incidence and mortality of prostate and testicular cancers, a diet rich in milk and cheese contributed to increased prostate cancer mortality rates [14]. In yet another ecological study a strong positive correlation was found between milk consumption and increased prostate cancer mortality [32]. Increased odds of developing prostate cancer with increased consumption of milk was observed in one study [33]. In another study though the study showed an increased odds of developing prostate cancer with increased consumption of milk, the intake of milk in midlife was neither associated with risk of prostate cancer nor advanced prostate cancer [34]. There was a positive relation between prostate cancer risk and milk or cheese consumption in one of the studies [35]. No association was observed between dairy products and risk of advanced or fatal prostate cancer [8]. Conversely, one large, prospective, population-based cohort study conducted in a Northern Sweden population failed to find an association between prostate cancer development and non-fermented or fermented milk consumption regardless of fat content [36]. Another study conducted in the United States suggested that there may be an association between 2% fat milk consumption and advanced prostate cancer, although the authors in this study suggested that this association may have occurred by chance.

DISCUSSION
The overwhelming majority of the studies included in this systematic review were suggestive of a link between milk consumption and increased risk of developing prostate cancer. Only one of the studies in this review did not show an association between milk consumption and increased risk for development of prostate cancer [34]. After conducting this systematic review, it is still unclear that the increased risk for prostate cancer is related to the dietary fat in the milk or non-fat components of the milk. While some studies found correlation between increased risk for prostate cancer and high fat content in the milk, others suggested that the non-fat components of the milk may be associated with the higher risk for the prostate cancer. Milk and dairy product are components of Western diet and it is possible that the increased risk for development of prostate cancer is related not to milk and dairy products in particular, but to overall carcinogenic effects of western diet.

Further research is needed to examine the relationship between dairy and dairy products consumption and the increased risk of development of prostate cancer. Ganmaa and colleagues [5] hypothesized that estrogens in milk may be related to the development of prostate cancer. High estrogen content in cow milk is a consequence of industrialized milk production [38]. While the hypothesis seems plausible, we were not able to find studies that evaluated the estrogen/estradiol content in the milk and its relation to the risk of developing prostate cancer. To add to this notion, there is a growing body of evidence that oestrogens may contribute to the development of prostate cancers [39]. Further research may confirm the estrogen/estradiol content in the dairy is related to the increased risk of prostate cancer or it will reject the hypothesis that high content milk estrogen may affect the risk for the development of prostate cancer. On the other hand, it may be beneficial to focus on non-fat components of the milk to further evaluate the effect of non-fat components on the risk of development of prostate cancer.

CONCLUSIONS
While the research finding are inconclusive clinicians may recommend to the patients who are at higher risk of prostate cancer development to eliminate or reduce the consumption of milk or milk products, especially those with high fat content. Such a decision should be made jointly with the patient and risks, benefits, and limitations of such a dietary approach should be discussed with the patient. If it is decided to eliminate or limit the consumption of milk products patient should be counseled about the appropriate calcium and vitamin D supplementation.

Prostate cancer is a complex disease with multifactorial origins that include, genetics, diet, and environmental influences. The risk reduction of the prostate cancer development may be achieved when all these
causative domains are fully understood and addressed.

Conflict of Interest

The authors have nothing to disclose.

Author Contribution

Conceptualization: all authors. Data curation: all authors. Methodology: all authors. Software: all authors. Validation: all authors. Writing – original draft: all authors. Writing – review & editing: all authors.

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