

Gallbladder Cancer and Its Association with Lifestyle Factors

Sudhanshu Sharma,¹ G.S.Shukla,² Virginia Paul,³

¹*Shalom Institute of Health & Allied Science, Sam Higginbottom University of Agriculture, Technology & Sciences (SHUATS), Allahabad, India*

²*Department of Health Sciences, UP Rajashri Tandon Open University Allahabad, India*

³*Ethlind School of Home Science, Sam Higginbottom University of Agriculture, Technology & Sciences (SHUATS), Allahabad, India*

Abstract

Gallbladder Cancer (GBC) is said to be most hidden or uncommon, but common amongst all gastrointestinal cancer and has very less survival rate. This cancer has very high incidences in north east part of India comparing the world. It's a well known saying "You can't control what goes on outside, but you CAN control what goes on inside." Apparently many aspects of our lifestyle factors for instance diet, obesity, lack of physical exercise, consumption of alcohol and tobacco contribute to the development of various diseases. This review will focus on the lifestyle factors which contribute to increase risk of gallbladder cancer and then on those additional protective factors which reduce cancer risk.

Keywords: *Gall bladder cancer, life style factors, food*

Introduction

It is estimated that almost 11,57,294 lakh people living in India are diagnosed with cancer every year and the number of people living with the disease are around 2.25 million. However due to considerable effect of modified lifestyle factors on the most preventable cancers, it has been known that 50% of cancers are preventable. The risk of developing cancer in a person depends on varied factors, including age, genetics, lifestyle and exposure to risk factors. The lifestyle factors include cigarette smoking, diet (fried foods, red meat, intake of vegetable fruits and fibre), alcohol, sun exposure, environmental pollutants, infections, stress, obesity, and physical inactivity (Anand et.al, 2008).

We often talk about the traits we receive from our father or mother. But in reality genes have very little role to play. Instead of our genes, our lifestyle and environment account for 90–95% of our most chronic illnesses (Anand et.al, 2018). Those Indian who have immigrated to western part of world have indicated that rates of cancer and other chronic diseases, such as coronary heart disease and diabetes, increase dramatically after a generation in the adopted country. There could be factors responsible like change of diet could modify the changing

disease rates(Sinha et al, 2003). Most cancers arise from a complex etiology involving genetic, environmental and lifestyle factors, and their interactions,(Cogliano et.al, 2011) and there is great need and opportunity for cancer prevention through lifestyle change.

Lifestyle plays an important role in carcinogenesis.

It has been estimated by the American Institute for Cancer Research and the World Cancer Research Fund that 30–40 percent of all cancers can be prevented by appropriate diets, physical activity, and maintenance of appropriate body weight (WCRF).

GBC is ranked 5th amongst all cancer in India especially in females. The incidence rate of Gallbladder Cancer (GBC) is even higher in North India compared to South India. Changes in life style choices of people have increased risk of GBC in recent years. It is highly deathly disease with poor prognosis. The diagnosis is commonly made at an advanced stage because of the uncertain signs and symptoms of disease. The overall mean survival rate for patients with advanced gallbladder cancer is 6 months, with a 5-year survival rate of 5% (Stinton and Shaffer, 2012).

For this reason in this review study the researcher tries to investigate the role of various lifestyle factors in the GBC. This review will focus on the lifestyle factors which contribute to increase risk of gallbladder cancer and also would enrich present available literature to enhance awareness of GBC, which would help to know additional protective factors which reduce cancer risk.

A literature search with a special emphasis on review article published in medical literature using search terms “gallbladder cancer OR Gallstones OR carcinoma and lifestyle factors” was performed. As part of a larger project on risk factors for gallbladder disease wide search terms such as body mass index OR overweight OR obesity OR physical activity OR inactivity OR smoking OR tobacco OR risk factor were used. Prospective studies that investigated the association between lifestyle factors and the risk of gallbladder disease were included. Secondary references obtained from these publications were identified by a manual search and reviewed as relevant. Case reports except for rare pathological entities were predominantly excluded. Considering that the articles discussing on GBC and its association with lifestyle factors were included in this review, in this way this study focuses on the lifestyle factors which contribute to increased risk of gallbladder cancer and then on those protective factors which when modifies helps in reducing cancer risk. Respectively selected relevant abstracts from ICMR (Indian Council of Medical Research) and other relevant organisations have also been reviewed. We have predominately limited our search to publications since 1990 to review concepts of gallbladder cancer in the 21st century.

Epidemiology ofGBC

GBC is been associated with a poor prognosis because of late diagnosis and few effective treatment choices. Patients with GBC usually have few symptoms or signs but can deteriorate rapidly due to the development of metastatic disease (Hueman et.al, 2009). Gallbladder cancer is about two to five times more common in women than in men. Little is known about the aetiology of this neoplasm besides a strong link with gallstones (Randiet al, 2006).

Incidences of GBC in other part of world and India can be clearly understood by the given map mentioned below which illustrates that how alarming situation is emerging for GBC in India



Incidence of GBC (From National Cancer Institute. Surveillance, Epidemiology and End Results (SEER) Program.
Source :<http://seer.cancer.gov>

Major Lifestyle Factors

Lifestyle factors play an important role in carcinogenesis. Lifestyle modification, particularly abstaining from smoking and tobacco chewing, healthy eating and physical activity may go a long way to prevent carcinogenesis in the gallbladder.

Obesity

Obesity has become a global health issue because of its great association with different diseases. It is widely acknowledged that being overweight increase the risk of morbidity and mortality. Overweight and obesity are defined as abnormal or excessive fat accumulation that

may impair health. Body mass index (BMI) is a simple index of weight-for-height that is commonly used to classify overweight and obesity in adults. It is one way to tell whether if a person is having a normal weight, is overweight, or has obesity. Weight gain occurs when energy intake persistently exceeds expenditure; whereas when increased energy intake is matched by increased energy expenditure, weight will remain stable. Below is a BMI to decide if a weight of a person is putting him at a risk of various health problems.

WHO CLASSIFICATION OF WEIGHT STATUS	
WEIGHT STATUS	BODY MASS INDEX (BMI), kg/m ²
Underweight	<18.5
Normal range	18.5 – 24.9
Overweight	25.0 – 29.9
Obese	≥ 30
Obese class I	30.0 – 34.9
Obese class II	35.0 – 39.9
Obese class III	≥ 40

Adapted from the 1998 WHO report "Report of a WHO consultation on obesity. Obesity: preventing and managing the global epidemic."

Overcons

umption of calories is one of the biggest key factors of obesity. In the United States Sixty-four percent of the adult population is overweight or obese (Vastag, 2004). It was estimated in a study, from a prospective cancer prevention cohort, that overweight and obesity accounted for 14 percent of all cancer deaths in men and 20 percent of those in women (Calle et.al 2003). According to an American Cancer Society study (Calle et.al, 2003), obesity has been associated with increased mortality from cancers of the colon, breast (in postmenopausal women), endometrium, kidneys (renal cell), esophagus (adenocarcinoma), gastric cardia, pancreas, prostate, gallbladder, and liver (Anand et.al, 2008). In over 84,000 men and 97,000 women included in the Cancer Prevention Study II Nutrition Cohort, the relative risk of GBC was 1.8 (95% confidence interval [CI], 1.1 to 2.9) in obese men with a Body Mass Index (BMI) of 30.0 to 34.9 compared to men with a normal BMI (18.5 to 24.9). Obese women (BMI, 30.0 to 34.9) had a relative risk of 2.1 (95% CI, 1.6 to 2.9) compared to women with a normal BMI (Calle, et.al, 2002). Overall, obesity has a relative risk of 1.66 (95% CI, 1.47 to 1.88) for gallbladder cancer (Larsson and Wolk, 2007). On considering men other lifestyle risks involve cigarette smoking, and alcohol consumption (Yagy, et.al, 2008). Obesity increases the risk for gallstones, and a history of gallstones appears to carry the highest risk of GBC. Gallbladder cancer risk was 15 and 66% higher among those who were overweight and obese, respectively, as compared with those of normal weight. The

association between obesity and gallbladder cancer risk was stronger in women than in men (Wang et.al, 2012)

It was estimated in a recent study, from a prospective cancer prevention cohort, that overweight and obesity accounted for 14 percent of all cancer deaths in men and 20 percent of those in women (Calle et.al, 2003). Significant positive associations were found between obesity and higher death rates for the following cancers: oesophagus, colon and rectum, liver, gallbladder, pancreas, kidney, stomach (in men), prostate, breast, uterus, cervix, and ovary (Calle et.al, 2003). The authors estimated that over 90,000 cancer deaths per year could be avoided if the adult population all maintained a normal weight (BMI < 25.0) (Calle et.al, 2003).

Smoking and Cancer

Smoking is believed to be associated with increased risk gallbladder cancer. It is one of the most common forms of recreational drug use. Tobacco smoking is the most popular form, being practiced by large people globally, of who the majority are in the developing countries. According to a report of US department of Health and Human Services (2010), every time a person takes a puff of a cigarette 7000 chemicals enter the lungs and spread to other parts of the body, including 69 known carcinogens. Smoking can cause cancer of lung, stomach, mouth and throat, kidney, pancreas, cervix, ovary, colorectal cancer.

Some research suggests that smoking increases the risk of developing gallstones. Gallstones form when liquid stored in the gallbladder turns into material that resembles stones. Further, as the incidence of gallstone disease escalates, there is a concomitant increase in complications like gallstone-related pancreatitis (Lindkvist, et.al, 2004). In order to analyse the association of cigarette smoking and GBC, a meta analysis was performed. The analysis of 11 studies found that smokers had an increased risk of GBC development, compared with nonsmokers (SRRs 1.45, 95% CIs, 1.11-1.89). There was moderate heterogeneity among studies ($Q=18.15$, $P=0.052$, $I^2=44.9\%$). These increased risks were independent of alcohol use and a history of gallstones (Wenbin et.al, 2013).

Tobacco and alcohol are established risk factors for several cancers (IARC, 2012)) and have been classified as group 1 carcinogens by the International Agency for Research on Cancer (Secretan, 2009).

A prospective study was conducted to evaluate the association of cigarette smoking and alcohol consumption with the risk of gallbladder cancer death. Study shows that smoking

elevated the risk of gallbladder cancer death. Among women, the hazard ratio (HR) [95 percent confidence interval: 95% CI] of current smoker was 2.00 [0.91–4.42], when adjusted for age and drinking. Among men, HR of current smoker was 2.27 [1.05–4.90]. HRs of those who smoked 21 cigarettes or more per day and those with 801–1,000 cigarette-years were 3.18 [1.18–8.53] and 3.44 [1.40–8.45], respectively, and positive linear associations were observed between that risk and the number of cigarettes per day (p for trend = 0.007) or “cigarette-years” (p for trend = 0.012). The alcohol dose was linearly associated with risk (p for trend = 0.004), where the HR among those who consumed 72.0 g or more of alcohol per day was 3.60 [1.29–9.85]. Among both men and women, cigarette smoking may elevate the risk of death from gallbladder cancer. Drinking may pose an elevated risk among men, but that seems to be less true among women (Yagyu, et.al, 2008).

Diet and cancer

Research suggests that people who follow a healthy diet have a lower risk of gallbladder disease. It is especially true for those people who have already experienced gallbladder problems to know what foods to consume and which ones to elude. Higher intake of energy and carbohydrate possibly increase the risk of GBC, conversely adequate intake of fruits and vegetables probably reduce the risk of GBC. This nutritional preventive effect against GBC could be attributed to high content of vitamins, carotenes and fibres. Apparently variety of essential nutrients can significantly modify the carcinogenic process. Findings in various studies on the consumption of vegetables indicate an inverse association with gallbladder cancer risk (Rai, et.al, 2004). The protective effect of vegetables and fruits on gallbladder cancer is also reported by Pandey et al (2002). There are many possible reasons given as to how a diet with a high consumption of vegetables and fruits prevents the occurrence of cancer. Possibly a large number of anti-carcinogenic agents i.e. carotenoids, vitamin C, vitamin E, selenium, folic acid, dietary fibre, indoles, phenols, flavinoids, protease inhibitors, allium compounds and plant sterols are found in these food sources.

It has been estimated by the American Institute for Cancer Research and the World Cancer Research Fund that 30–40 percent of all cancers can be prevented by appropriate diets, physical activity, and maintenance of appropriate body weight (WCRF). There is no specific diet for a healthy gallbladder, but following some guidelines can help keep the gallbladder healthy and functioning well. It has been analysed that obesity, nutrient sparse foods such as concentrated sugars and refined flour products that contribute to impaired glucose metabolism (which leads to diabetes), low fibre intake, consumption of red meat, and

imbalance of omega 3 and omega 6 fats all contribute to excess cancer risk (Donaldson, 2004). The study also states that there are few protective diet which help in prevention of cancer these include selenium, folic acid, vitamin B-12, vitamin D, chlorophyll, and antioxidants such as the aryteneoids (α -carotene, β -carotene, lycopene, lutein, cryptoxanthin). Dietary factors have been thought to account for about 30% of cancers in Western countries, making diet second only to tobacco as a preventable cause of cancer (TJ Key, 2004).

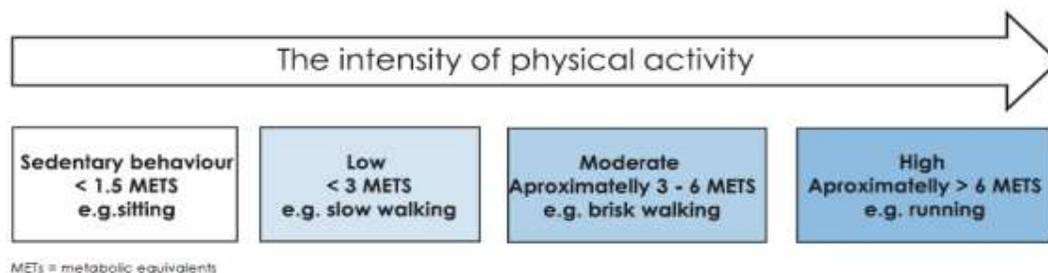
A history of gallstones appears to carry the highest risk of GBC. It has been established that gallstones are associated with GBC. However, there is no evidence of a direct causal relationship between gallstones and GBC (ICAR). There is no one food or group of foods that will eradicate gallstones. Nonetheless, eating a healthful diet with limited saturated fat and refined carbohydrates is healthful and might help. Low intake of dietary fibre has been suggested as a possible cause of a variety of disorders prevalent among western societies including cholesterol gallstones. A higher intake of fibre is associated with fewer gallstones. Unhealthy eating habits could increase the risk of cancer as much as drinking alcohol; this is because what we eat and drink affects our health in various ways. Diet has great impact on our weight, if we take healthy diet, we can keep a healthy weight which reduces the risk of cancer. High in plant food diet – such as fruit, vegetables, whole grains and beans helps in maintaining healthy weight, and may also protect against certain cancers. The high-fibre diet can help stay at a healthy weight which in turn, lowers risk for many kinds of cancer. Eating fast foods such as chips and fried chicken or other processed foods that are high in fat and sugar like chocolate and bakery products can lead to weight gain and there is strong evidence that being overweight is a cause of cancer.

Physical Activity and cancer

Physical activity can be defined as any movement that uses skeletal muscles and requires more energy than resting it includes walking, running, dancing, biking, swimming, performing household chores, exercising, and engaging in sports activities. Studies show the strong evidence that physical inactivity increases the risk of cancer. Furthermore, inactivity and obesity together account for risk of several major cancers. Sedentary behaviour such as sitting, reclining, or lying down for extended periods of time is a risk factor for developing the risk of many cancers. Exercise on other hand has many biological effects on the body. Physical activity can also reduce cancer risk mediated through obesity, since obesity is associated with increased risk of developing as many as 13 cancer types through similar biological mechanisms (Patel et.al, 2019).

The International Agency for Research on Cancer (IARC) reports that 25% of all cancer cases worldwide are caused by obesity and sedentary lifestyle (Vainer et.al, 2002). Correspondingly, studies also indicate that physical activity may reduce the advancement of cancer, its re-occurrence and have an impact on better survival rates (Assi et.al, 2020). The American Cancer Society (ACS), the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) and the World Health Organization (WHO) have published recommendations considered to reduce the risk of various diseases including cancer (Coletta et.al, 2019). In summary, the recommendations for adults of 150 minutes (2.5h) to 300 minutes (5h) of moderate physical activity, or at least 75 minutes (1.25 hours) to 150 minutes (2.5h) of vigorous physical activity per week, can reduce cancer risk. For additional health benefits, muscle-strengthening activities involving major muscle groups should be conducted on two or more days a week (Ainsworth et.al, 2000).

The intensity level of physical activity is measured as, the rate of energy expenditure expressed in metabolic equivalents (METs). In epidemiological studies the MET model provides general medical thresholds and guidelines for a population (Matthews et.al, 2020). One MET is the rate of energy expenditure while sitting at rest, which for most people approximates an oxygen uptake of 3.5 millilitres per kilogram of body weight per minute. The energy expenditure of other activities is expressed in multiples of METs. A 3 MET activity expends 3 times the energy used at rest.



<https://www.ncbi.nlm.nih.gov/pmc/articles/instance/7877262/bin/raon-55-007-g001.jpg>

To determine the association of leisure-time physical activity with incidence of common types of cancer researchers examined leisure-time physical activity in relation to risk of 26 different cancer types in a pooled analysis of 12 prospective cohort studies and 1.44 million participants. A higher level of leisure-time physical activity was associated with lower risk for 13 of the 26 types of cancer. Compared with a lower level of leisure-time physical activity (10th percentile), higher level of activity (at the 90th percentile) had strong inverse associations (greater than 20% reduction in risk) for 7 cancers. Suggestive inverse associations were also noted for gallbladder cancer (HR, 0.72 [95% CI, 0.51-1.01]). The study also systematically explores the role of BMI in physical activities association with the full spectrum of cancer types. Findings of the study support promoting physical activity as a key component of population-wide cancer prevention and control efforts (Moore et.al, 2009)

Conclusion

On reviewing different relevant article it shows that GBC is fast growing upper gastrointestinal cancer in last 2 decades. Lifestyle factors are the predominant factor for its high incidences are gallbladder diseases. It has been seen that some major diet association have some relation to increase incidences of GBC e.g. consumption of fibre, Fat, sugar, egg, etc. In this review we have concluded that there is an important relation between dietary factors and gallbladder cancer. Overconsumption of food rich in energy and carbohydrate possibly increase the risk of GBC and adequate intake of fruits and vegetables probably reduce the risk of GBC. Fruits and vegetables may have several potentially anticarcinogenic agents.

At least two-thirds of the cases of cancer are caused by environmental factors and many linked to lifestyle factors. Lifestyle factors can be modified, such as cigarette smoking, excessive alcohol consumption, poor diet, physical inactivity, and being overweight or obese. Large number of cancer deaths could be prevented by eliminating the use of unhealthy products. After tobacco, obesity appears to be the most important preventable cause of cancer. To reduce the risk of developing gallbladder cancer the advice is that people should:

Obesity predisposes to many health problems. The incidence of obesity has risen substantially over the recent years; on this ground a greater public awareness of the potential health threat associated with obesity is clearly needed. Maintain a healthy weight. Being physically active and maintaining a healthy weight and eating a healthy diet is prime important for preventing cancer in general.

The use of tobacco products is linked to many cancers. Study suggests that smoking and alcohol increases the risk of gallbladder cancer dose-dependently among both men and women. This research indicates a probable role of tobacco chewing, smoking, alcohol consumption, physical inactivity, as the lifestyle factors in the causation of carcinoma. Amongst all cancer disease the fundamental concept to prevent it, is adopting better life style which includes more of physical activity and less of mental stress, a healthy diet. As GBC itself is said to be most hided cancer among all, hence regular check up with ultrasound of abdomen can better help for early diagnosis of disease and easy intervention and treatment is possible.

References

- Ainsworth, B. E., Haskell, W. L., Whitt, M. C., Irwin, M. L., Swartz, A. M., Strath, S. J., . . . Leon, A. S. (2000September). Compendium of physical activities: An update of activity codes and MET intensities. *Medicine and Science in Sports and Exercise*, 32(9)(Suppl.), S498–S504. doi:[10.1097/00005768-200009001-00009](https://doi.org/10.1097/00005768-200009001-00009), PubMed: [10993420](https://pubmed.ncbi.nlm.nih.gov/10993420/)
- Assi, M., Dufresne, S., & Rébillard, A. (2020). Exercise shapes redox signaling in cancer. *Redox Biology*, 35, 101439. doi:[10.1016/j.redox.2020.101439](https://doi.org/10.1016/j.redox.2020.101439)
- Calle, E. E., Rodriguez, C., Jacobs, E. J. et al. (2002). The American Cancer Society Cancer Prevention Study II Nutrition Cohort: Rationale, study design, and baseline characteristics. *Cancer*, 94, PubMed: [24902501](https://pubmed.ncbi.nlm.nih.gov/24902501/)
- Calle, E. E., Rodriguez, C., Walker-Thurmond, K., & Thun, M. J. (2003). Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *New England Journal of Medicine*, 348(17), 1625–1638. doi:[10.1056/NEJMoa021423](https://doi.org/10.1056/NEJMoa021423)
- Cogliano, V. J., Baan, R., Straif, K., Grosse, Y., Lauby-Secretan, B., El Ghissassi, F., . . . Wild, C. P. (2011). Preventable exposures associated with human cancers. *Journal of the National Cancer Institute*, 103(24), 1827–1839. doi:[10.1093/jnci/djr483](https://doi.org/10.1093/jnci/djr483)
- Coletta, A. M., Marquez, G., Thomas, P., Thoman, W., Bevers, T., Brewster, A. M., . . . Gilchrist, S. C. (2019). Clinical factors associated with adherence to aerobic and resistance physical activity guidelines among cancer prevention patients and survivors. *PLOS ONE*, 14(8), e0220814. doi:[10.1371/journal.pone.0220814](https://doi.org/10.1371/journal.pone.0220814)
- Indian Council of Medical Research. (2014). Consensus document for management of gallbladder cancer. Prepared as an outcome of ICMR Subcommittee on gallbladder Cancer, 2014. Published by the Division of Publication and Information on behalf of the Secretary. DHR & DG. New Delhi: Indian Council of Medical Research.
- Dhir, V., & Mohandas, K. M. (1999). Epidemiology of digestive tract cancers in India IV. Gall bladder and pancreas. 2. *Indian Journal of Gastroenterology*, 18(1), 24–28.
- Donaldson, M. S. (2004). Nutrition and cancer: A review of the evidence for an anti-cancer diet. *Nutrition Journal*, 3, 19. doi:[10.1186/1475-2891-3-19](https://doi.org/10.1186/1475-2891-3-19)
- Hueman, M. T., Vollmer, C. M., Jr., & Pawlik, T. M. (2009). Evolving treatment strategies for gallbladder cancer. *Annals of Surgical Oncology*, 16(8), 2101–2115. doi:[10.1245/s10434-009-0538-x](https://doi.org/10.1245/s10434-009-0538-x)
- IARC working group on the evaluation of carcinogenic risks to humans. Personal habits and indoor combustions. (2012); 100(pt E). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, 100e. A review of human carcinogens, 1–538.
- Larsson, S. C., & Wolk, A. (2007May). Obesity and the risk of gallbladder cancer: A meta-analysis. *British Journal of Cancer*, 96(9 (9)), 1457–1461. doi:[10.1038/sj.bjc.6603703](https://doi.org/10.1038/sj.bjc.6603703)
- Lindkvist, B., Appelros, S., Manjer, J., & Borgström, A. (2004). Trends in incidence of acute pancreatitis in a Swedish population: Is there really an increase? *Clinical Gastroenterology and Hepatology*, 2(9), 831–837. doi:[10.1016/s1542-3565\(04\)00355-6](https://doi.org/10.1016/s1542-3565(04)00355-6)

- Matthews, C. E., Moore, S. C., Arem, H., Cook, M. B., Trabert, B., Håkansson, N. (2020). Amount and intensity of leisure-time physical activity and lower cancer risk. *Journal of Clinical Oncology*, 38(7), 686–697. doi:[10.1200/JCO.19.02407](https://doi.org/10.1200/JCO.19.02407). et al.
- Moore, S. C., Lee, I. M., Weiderpass, E., Campbell, P. T., Sampson, J. N., Kitahara, C. M., . . . Patel, A. V. (2016 June 1). Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults. *JAMA Internal Medicine*, 176(6), 816–825. doi:[10.1001/jamainternmed.2016.1548](https://doi.org/10.1001/jamainternmed.2016.1548), PubMed: [27183032](https://pubmed.ncbi.nlm.nih.gov/27183032/), PubMed Central: [PMC5812009](https://pubmed.ncbi.nlm.nih.gov/PMC5812009/)
- Murthy, N. S., Rajaram, D., Gautham, M. S. et al. (2011). Trends in incidence of gallbladder cancer—Indian scenario. In *Gastrointestinal Cancer: Targets and Therapy*, 1, 1–9.
- Pandey, M., & Shukla, V. K. (2002). Diet and gallbladder Cancer: A case control study. *European Journal of Cancer Prevention*, 11(4), 365–368. doi:[10.1097/00008469-200208000-00008](https://doi.org/10.1097/00008469-200208000-00008)
- Patel, A. V., Friedenreich, C. M., Moore, S. C., Hayes, S. C., Silver, J. K., Campbell, K. L., . . . Matthews, C. E. (2019). American College of Sports Medicine roundtable report on physical activity, sedentary behavior, and cancer prevention and control. *Medicine and Science in Sports and Exercise*, 51(11), 2391–2402. doi:[10.1249/MSS.0000000000002117](https://doi.org/10.1249/MSS.0000000000002117)
- Anand, P., Kunnumakkara, A. B., Sundaram, C., Harikumar, K. B., Tharakan, S. T., Lai, O. S., . . . Aggarwal, B. B. (2008). Cancer is a preventable disease that requires major lifestyle changes. *Pharmaceutical Research*, 25(9), 2097–2116. doi:[10.1007/s11095-008-9661-9](https://doi.org/10.1007/s11095-008-9661-9)
- Rai, A., Mohapatra, S. C., & Shukla, H. S. (2004). A review of association of dietary factors in gallbladder cancer. *Indian Journal of Cancer* [serial online], 41, 147–151.
- Randi, G., Franceschi, S., & La Vecchia, C. (2006). Gallbladder cancer worldwide: Geographical distribution and risk factors. *International Journal of Cancer*, 118(7), 1591–1602. doi:[10.1002/ijc.21683](https://doi.org/10.1002/ijc.21683)
- Secretan, B., Straif, K., Baan, R., Grosse, Y., El Ghissassi, F., Bouvard, V., . . . WHO International Agency for Research on Cancer Monograph Working Group. (2009). A review of human carcinogens—Part E: Tobacco, areca nut, alcohol, coal smoke, and salted fish. *Lancet. Oncology*, 10(11), 1033–1034. doi:[10.1016/s1470-2045\(09\)70326-2](https://doi.org/10.1016/s1470-2045(09)70326-2)
- Secretan, B., Straif, K., Baan, R., Grosse, Y., El Ghissassi, F., Bouvard, V., . . . WHO International Agency for Research on Cancer Monograph Working Group. (2009). A review of human carcinogens—Part E: Tobacco, areca nut, alcohol, coal smoke, and salted fish. *Lancet Oncology*, 10(11), 1033–1034. doi:[10.1016/S1470-2045\(09\)70326-2](https://doi.org/10.1016/S1470-2045(09)70326-2)
- Sinha, R., Anderson, D. E., McDonald, S. S., & Greenwald, P. (2003). Cancer risk and diet in India. *Journal of Postgraduate Medicine*, 49(3), 222–228.
- Stinton, L. M., & Shaffer, E. A. (2012). Epidemiology of gallbladder disease: Cholelithiasis and cancer. *Gut and Liver*, 172–87, 6(2, April), 11722–11197. Retrieved from <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3343155/pdf/gnl-6-172.pdf>. doi:[10.5009/gnl.2012.6.2.172](https://doi.org/10.5009/gnl.2012.6.2.172)
- Key, T. J., Schatzkin, A., Willett, W. C., Allen, N. E., Spencer, E. A., & Travis, R. C. (2004). Diet, nutrition and the prevention of cancer. *Public Health Nutrition*, 7(1A), 187–200. doi:[10.1079/phn2003588](https://doi.org/10.1079/phn2003588)

- Vainio, H., Kaaks, R., & Bianchini, F. (2002). Weight control and physical activity in cancer prevention: International evaluation of the evidence. *European Journal of Cancer Prevention*, 11(Suppl. 2), S94–S100.
- Vastag, B. (2004). Obesity is now on everyone's plate. *JAMA*, 291(10), 1186–1188.
doi:[10.1001/jama.291.10.1186](https://doi.org/10.1001/jama.291.10.1186)
- Wang, F., Wang, B., & Qiao, L. (2012 June 1). Association between obesity and gallbladder cancer. *Frontiers in Bioscience (Landmark Edition)*, 17, 2550–2558. doi:[10.2741/4070](https://doi.org/10.2741/4070), PubMed: [22652797](https://pubmed.ncbi.nlm.nih.gov/22652797/)
- WCRF/AICR. *Food, nutrition and the prevention of cancer: A global perspective*. World Cancer Research Fund / American Institute for Cancer Research 1997.
- Wenbin, D., Zhuo, C., Zhibing, M., Chen, Z., Ruifan, Y., Jie, J., . . . Zhenming, G. (2013 March). The effect of smoking on the risk of gallbladder cancer: A meta-analysis of observational studies. *European Journal of Gastroenterology and Hepatology*, 25(3), 373–379.
doi:[10.1097/MEG.0b013e32835a870b](https://doi.org/10.1097/MEG.0b013e32835a870b)
- Yagyu, K., Kikuchi, S., Obata, Y., Lin, Y., Ishibashi, T., Kurosawa, M., . . . JACC Study Group. (2008). Cigarette smoking, alcohol drinking and the risk of gallbladder cancer death: A prospective cohort study in Japan. *International Journal of Cancer*, 122(4), 924–929. doi:[10.1002/ijc.23159](https://doi.org/10.1002/ijc.23159)
- Yagyu, K., Kikuchi, S., Obata, Y., Lin, Y., Ishibashi, T., Kurosawa, M., . . . JACC Study Group. (2008 February 15). Cigarette smoking, alcohol drinking and the risk of gallbladder cancer death: A prospective cohort study in Japan. *International Journal of Cancer*, 122(4), 924–929.
doi:[10.1002/ijc.23159](https://doi.org/10.1002/ijc.23159), PubMed: [17955487](https://pubmed.ncbi.nlm.nih.gov/17955487/)