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Association of *ABCG5* and *ABCG8* Polymorphisms with Gallstone Disease and Gallbladder Cancer

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Aim: to analyze the role of nucleotide sequence variants (NSVs) of *ABCG5* and *ABCG8* genes in gallstone disease (GSD) and gallbladder cancer (GBC).
Key points. ABCG5 and ABCG8 are key sterol efflux transporters that regulate hepatic secretion and intestinal absorption of cholesterol. *ABCG5/G8* is the human *LITH9* gallstone gene. One of the major genetic risk factors for GSD rs11887534 (D19H) *ABCG8*, as a 'gain-of-function' NSV, increases the activity of this transporter by 3.2 times, which leads to supersaturation of bile with cholesterol and an increased risk of GSD. On average, rs11887534 increases the risk of GSD in children by 4 times, in adults — by 2 times, which has been proven in population, genome-wide studies and meta-analyses worldwide. The presence of the H allele D19H (rs11887534) is associated with a two-fold risk of recurrence of GSD after cholecystectomy. The results of the studies of the associations of GSD with other NSVs of *ABCG8* (T400K, A632V, M429V, C54Y) and *ABCG5* (E604Q, R50C) genes are contradictory.
In population studies, rs11887534 was associated with a 4-fold increase in the risk of GBC, and the risk is more prominent (4.9 times) in patients with GBC and gallstones. We found no studies of the NSVs of the *ABCG5* and *ABCG8* genes in biliary pathology in Russia.
Conclusion. Most studies confirm the role of the rs11887534 *ABCG8* gene as a predictor of GSD and GBC; however, replicating studies of NSVs of *ABCG5* and *ABCG8* genes in biliary pathology in Russia are needed.
Keywords: gallstone disease, gallbladder cancer, NSV, *ABCG5*, *ABCG8*, rs11887534
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Ассоциация полиморфизма *ABCG5* и *ABCG8* с желчнокаменной болезнью и раком желчного пузыря

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Цель обзора: анализ роли вариантов нуклеотидной последовательности (ВНП) генов *ABCG5* и *ABCG8* при желчнокаменной болезни (ЖКБ) и раке желчного пузыря (РЖП).
Основные положения. Транспортеры оттока стеролов *ABCG5* и *ABCG8* имеют ключевое значение в печеночной секреции и кишечной абсорбции холестерина. *ABCG5/G8* представляет собой человеческий ген желчных камней *LITH9*. Один из основных генетических факторов риска ЖКБ rs11887534 (D19H) *ABCG8* как ВНП с «приобретением функции» повышает активность транспортера в 3,2 раза, что приводит к перенасыщению желчи холестерином и увеличению риска ЖКБ. В среднем rs11887534 повышает риск ЖКБ у детей в 4 раза, у взрослых — в 2 раза, что доказано в популяционных полногеномных исследованиях и в метаанализах во всем мире. Наличие аллеля H D19H (rs11887534) связано с двукратным риском рецидива ЖКБ после

холецистэктомии. Результаты исследований связи ЖКБ с другими ВНП генов *ABCG8* (T400K, A632V, M429V, C54Y) и *ABCG5* (E604Q, R50C) являются противоречивыми.
В популяционных исследованиях rs11887534 связан с 4-кратным повышением риска РЖП, причем риск более выражен (в 4,9 раза) у больных РЖП с камнями в желчном пузыре. Мы не обнаружили исследований ВНП генов *ABCG5* и *ABCG8* при билиарной патологии в России.
Заключение. В большинстве исследований подтверждена роль rs11887534 гена *ABCG8* как предиктора ЖКБ и РЖП, однако требуются реплицирующие исследования ВНП генов *ABCG5* и *ABCG8* при билиарной патологии в России.
Ключевые слова: желчнокаменная болезнь, рак желчного пузыря, ВНП, *ABCG5, ABCG8*, rs11887534
Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.
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Introduction

The ATP-binding cassette (ABC) transport proteins have been studied for over 50 years. In 1986, they were grouped into one of the largest families of membrane proteins that transport multiple substrates. They are now represented by 48 proteins, which are divided into seven subfamilies (A–G) [1, 2]. In humans, the functions of ABC proteins are diverse and provide numerous key (patho) physiological processes, making them causative factors in a number of diseases: sitosterolemia, coronary heart disease (CHD), gallstone disease (GSD), atherosclerosis, intrahepatic cholestasis, cystic fibrosis, Tangier disease, malignant neoplasms, etc. [1, 3–6].

Characteristics of the *ABCG5/ABCG8* sterol transporter proteins

ABCG5/8 onsists of the G5 and G8 polypeptides, in humans, the ABCG5/G8 sterol efflux transporter genes are co-localized on chromosome 2p21 [2]. Although ABCG8 functions as a transporter in concert with ABCG5, G5 and G8 differ in signature motifs and missense mutations associated with gallstone formation [7]. The two proteins transport neutral sterols from hepatocytes and enterocytes into bile and the intestinal lumen, respectively, and can simultaneously reduce plasma cholesterol levels and increase biliary cholesterol excretion [4, 8, 9]. ABCG5/G8 proteins play a key role in maintaining cholesterol homeostasis in the body by regulating hepatic secretion of biliary cholesterol; intestinal absorption of cholesterol; reverse cholesterol transport; transintestinal excretion of cholesterol [2], which, for example, can reduce the cardiovascular risk [2, 4].

In the liver (with the participation of many factors, including apolipoproteins), cholesterol is mainly converted into bile salts, which reduces its concentration in plasma and improves the elimination of excess cholesterol from the body [2, 10]. Supersaturation of bile with cholesterol is a key point in the formation of gallstones [11], therefore, the important role of ABCG5/G8 protein genes as transporters of sterol outflow from hepatocytes into bile determined the **aim of the study** — to analyze the role of nucleotide sequence variants (NSVs) of the *ABCG5* and *ABCG8* genes in GSD and gallbladder cancer (GBC).

We analyzed and evaluated studies describing the analysis of the association between the ABCG5 and ABCG8 genes and biliary pathology in the PubMed, PubMed Central (PMC), OMIM, Google Scholar and Russian Science Citation Index (RSCI) databases from 1980 to 2024. A MeSH text and title search strategy with various combinations of the phrases “ABCG5/G8 functions”, “ABCG5/G8 polymorphism”, “ABCG5 or ABCG8 variants”, “rs11887534”, “GSD”, or “gallbladder cancer” in combination with “ABCG5/G8”, “ABCG5”, or “ABCG8” was used to select studies. We excluded articles on hematological causes of GSD from the analysis.

Briefly about GSD and its genetic predisposition

In the 21st century, GSD occurs in 10–20 % of the population in economically developed countries and it is estimated that about 1 million new cases of the disease are diagnosed each year [2]. In our studies of GSD, along with other numerous results, we also confirmed the importance of the main risk factors for GSD in cholelithogenesis — female gender, age, excess weight, the presence

of concomitant diseases, such as coronary heart disease [12], arterial hypertension [13], hereditary burden and genetic factors — polymorphisms of the genes *APOE, IL-1β, TNF-α, TRPM8, ADRB1* [13–15] and we plan to study the role of rs11887534 of the *ABCG8* gene. Genetic predisposition to GSD has been substantiated in many studies [16–20]: the familial nature of GSD confirms a 2–3-fold increase in the risk of the disease among first-degree relatives [18, 19] and in studies of twins, the overall risk of developing gallstones is estimated at 25–29 % [19, 20].

Characteristics of rs11887534 in the *ABCG8* gene

By 2023, more than 700 missense variants have been identified for the *ABCG5* and *ABCG8* genes according to the PubMed website (PubMed.gov) [6]. Most missense variants are benign, whereas most dysfunctional alleles in selected likely pathogenic *ABCG5/G8* missense mutants are dysfunctional due to their inability to heterodimerize ABCG5 and ABCG8 and translocate outside the endoplasmic reticulum [8].

The D19H NSV of the *ABCG8* gene, also designated rs11887534 (this is the specific NSV number in the SNP database catalog), is a missense variation in which the negatively charged amino acid histidine is replaced by the positively charged aspartic acid (G to C change) [16, 17]. Thus, the contribution of the genotype to GSD compared to the reference ("wild") genotype DD is: ABCG8 D19H, DD = 0, HH = 3.2, i.e. homozygotes for the minor ("mutant") H allel have a 3.2-fold increased risk of GSD [4]. NSV rs11887534 may affect the function of the ABCG8 transporter protein, leading to gallstone formation at an earlier age [21, 22]: the lithogenic H allele *ABCG8* D19H was present in 14.9 % of children with gallstones and was found in this cohort three times more often compared to children in the control group (frequency — 5.2 %); in children carriers, the odds ratio (OR) for developing GSD was 4.04 ($p < 0.01$), compared to the control group of children who were not carriers of H allele, the similar OR in adults was 1.90 ($p < 0.01$) [23]. The authors confirmed that the lithogenic variant rs11887534 is associated with increased cholesterol transport (or decreased absorption), possibly in combination with increased cholesterol synthesis in the liver, which may contribute to gallstone formation in carriers of the risk variant [23]. A Swedish study of monozygotic twins confirmed that, compared with the "stone-free" controls (9.4 %), 20.8 % of twins with gallstones were carriers of rs11887534, which increased the risk of gallstones by 2.5 times [24].

Experimental evidence in support of this hypothesis was obtained from the study of lithogenic loci in mice, which are localized together with approximately 27 "probable" candidate genes for GSD: thus, using QTL (quantitative trait locus mapping) studies, the *ABCG5/G8* gene was identified as a new human lithogenic gene *LITH9* [25].

NSV rs11887534 in GSD

Single nucleotide polymorphism D19H ABCG8 (rs11887534) is the most common (minor allele frequency H is more than 5 %), well-studied [2–6, 9, 16, 17, 21–29, 31–43], and a strong genetic risk factor for GSD, comparable in magnitude to known risk factors such as female gender, obesity [4, 23, 27].

The first genome wide association study (GWAS) of GSD (2007) identified rs11887534 as associated with GSD: a two-fold increase in the risk of GSD was found in carriers of H allele of D19 (OR = 2.2; $P = 1.4 \times 10^{-14}$) [16, 33], which is similar to the population risk of about 11 %, and the association was stronger in patients with cholesterol gallstones, suggesting that rs11887534 is associated with increased efficiency of cholesterol transport into bile [16]. A large-scale GWAS meta-analysis (2016) (8,720 GSD cases and 55,152 controls) confirmed the role of rs11887534 in gallstone susceptibility (OR = 1.69; $P = 2.44 \times 10^{-60}$) [34].

The *ABCG8* D19H gene NSV (rs11887534) is considered a "gain-of-function" mutation [23] (Fig. 1): the D19H H allele increases the transport activity of the *ABCG5/G8* lithogenic locus by 3.2-fold [28], including cholesterol efflux into bile, and therefore leads to bile supersaturation and the development of GSD [4], while carriers of the D19H H allele have lower levels of cholesterol [42] and sterols in serum [30] and a lower incidence of myocardial infarction: OR for myocardial infarction is 0.83 (i.e., a 17 % lower risk) [4]. Conversely, genetic variation associated with reduced ABCG5/G8 activity protects against gallstones [4].

The presence of the D19H H allele (rs11887534) is associated with a two-fold risk of recurrence of GSD more than six months after cholecystectomy: in a cohort study of 2308 people in a multivariate analysis for this allele (OR = 1.97; $p = 0.034$) [29], that is, the presence of the risk allele can additionally enhance the lithogenic predisposition in people already suffering from GSD [23].

The relationship between cholesterol levels in the blood and in bile is of clinical significance, since drugs that lower LDL cholesterol (statins, fibrates, ezetimibe) can act on the cholesterol concentration in bile in the opposite way, based on

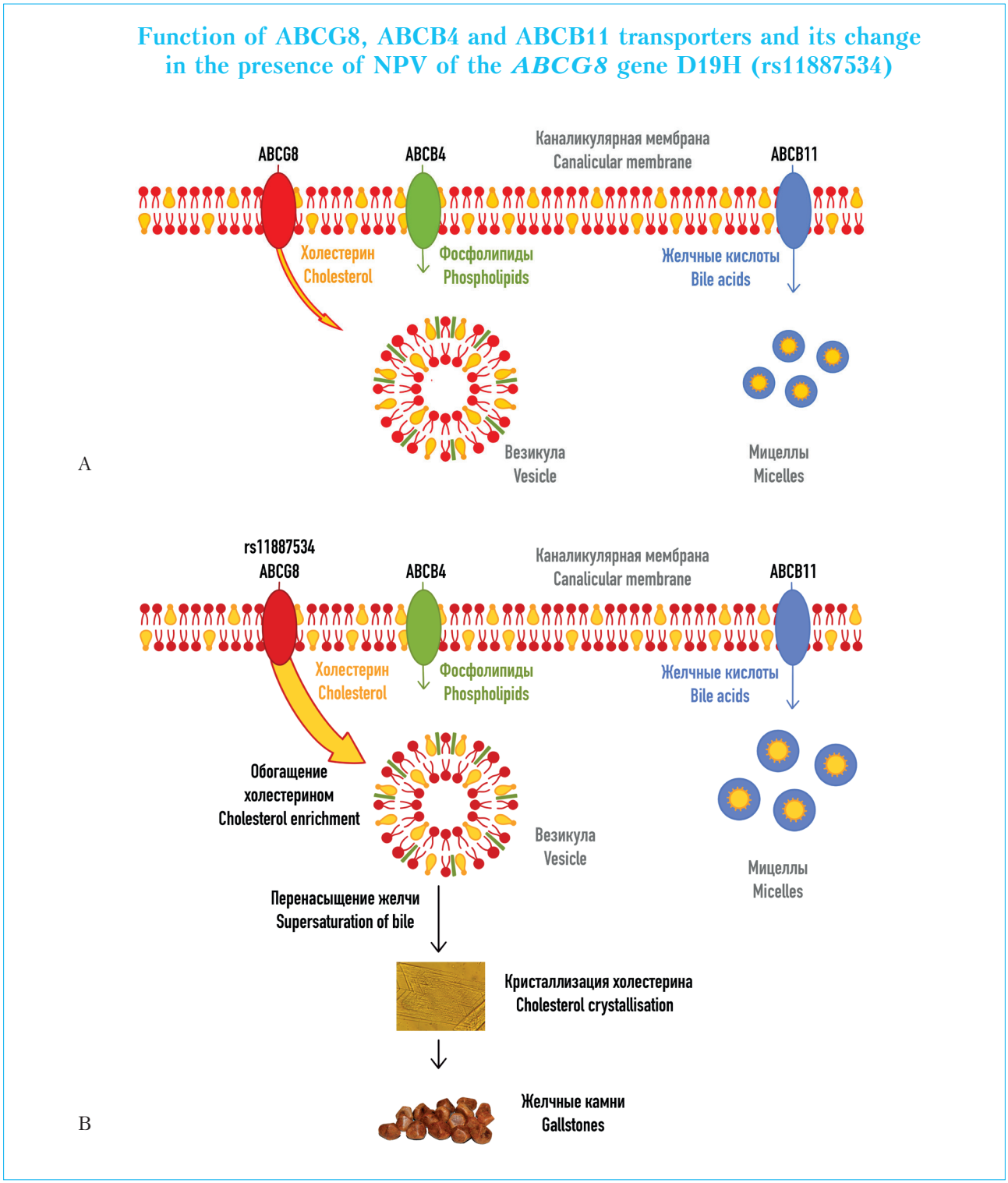

Figure. A — normally, cholesterol, phospholipids, and bile acids are secreted by located on the canalicular membrane ABCG8, ABCB4, and ABCB11 transporters, respectively, from the hepatocytes into the bile. Cholesterol is insoluble in water, bile vesicles and micelles transport cholesterol in bile; B — in NSV rs11887534 *ABCG8*, the outflow of cholesterol into bile increases, gallstones are formed. ABC — ATP-binding cassette (transporter)

Рисунок. А — в норме холестерин, фосфолипиды и желчные кислоты секретируются расположенными на каналикулярной мембране транспортерами ABCG8, ABCB4 и ABCB11, соответственно, из гепатоцитов в желчь. Холестерин нерастворим в воде, желчные везикулы и мицеллы осуществляют транспорт холестерина в желчи; В — при ВНП rs11887534 *ABCG8* увеличивается отток холестерина в желчь, образуются желчные камни. ABC — АТФ-связывающая кассета (транспортер)

whether they increase or decrease the cholesterol excretion into bile through ABCG5/G8 and, as a result, either protect against GSD (statins) or increase its risk (ezetimibe and fibrates) [4].

It is believed that the effect of *ABCG5/G8* VNSs on gallstone formation is mediated by an increase in expression of LXR-alpha (liver X receptor alpha) [31].

Taking into account geographic and ethnic differences in the prevalence of GSD, the association of rs11887534 with an increased risk of GSD has been research and proven in studies in the population of Europe, Asia, and America: in the USA [2, 3], Finland [8], Poland [23], Germany [22, 29], Sweden [24], Denmark [26], Chile, China [28, 31, 32], Latin America [35], India [36, 37], Taiwan [21, 38], Iran [39], Canada [40] and in meta-analyses [16, 34, 41, 43]. On average, rs11887534 increases the risk of GSD by 2 times, which has been proven in population (OR = 1.80–4.04), genome-wide studies (OR = 1.70–2.20) and meta-analyses (OR = 1.89–2.40) worldwide.

Other *ABCG8* gene NSVs associated with GSD

In the ABCG5/8 locus, the 19H allele is not the only lithogenic variant. For other ABCG8 gene NSVs (T400K, A632V, M429V, C54Y), some studies have confirmed an association with GSD in humans [6, 21, 40, 43, 44], while others have not: T400K [21, 37, 43], T400K and Y54C [41], A632V [21, 44].

ABCG5 gene NSVs associated with GSD

Carriers of the Q604E *ABCG5* gene NSV (rs6720173) have an increased risk of developing GSD regardless of age, gender, and body mass index [21, 42]. The association with GSD has been confirmed for the *ABCG5* R50C gene NSV (OR = 1.89) [2, 28, 33]. NSVs rs11887534 and rs6720173 are significantly associated with the lipid profile of lithogenic blood plasma in 34 pairs of brothers and sisters with GSD [42].

NSV rs11887534 associated with GBC

Compared to malignant tumors of the gastrointestinal tract of other localizations, such as pancreatic cancer [45], GBC is the least studied. GBC is rare in developed countries: for example, in the USA, less than 5,000 cases are registered per year [46], probably partly due to the high frequency of cholecystectomies for GSD worldwide – more than 1 million surgical interventions per year worldwide [2]. Worldwide, GBC has a low mortality rate, but some geographic areas have high mortality rates, especially among women, such as up to 21.5/100,000 in Northern India [47, 48]. The presence of gallstones is associated with the highest risk of GBC (relative risk – 4.9) [48].

The increased risk of developing biliary tract cancer is promoted by: NSV of the *ABCG8* gene, genes involved in lipid metabolism [49], NSV in the genes of toll-like receptors TLR2 and TLR4, cytochrome P450 1A1 (CYP1A1), tumor suppressor gene *TP53*, etc. [46]. In the Indian population, the frequency of rs11887534 was 1.79 times higher in patients with GBC, and the risk was more pronounced – 1.85 times – in patients with GBC with gallstones [50]. Two population studies have shown that rs11887534 is associated with a 2–4-fold increase in the risk of GBC [25, 32, 35].

It is possible that rs11887534 leads to increased gallstone formation, subsequent inflammation, and therefore susceptibility to GBC, but cancer by its nature requires multiple genetic changes, and peculiar properties of the contribution of this NSV remains to be studied. For example, a GWAS found a strong association between GBC risk and common NSVs in the chromosomal region 7q21.12 responsible for the *ABCB1* and *ABCB4* genes in India [51] and *ABCB4* in Chile [52]. It is also unclear whether rs11887534 alters the xenosterol species that are concentrated in bile, leading to gallstone formation, long-term inflammation, production of genotoxic agents, and then tumorigenesis.

The question remains open as to what additional lithogenic risk factors are necessary to increase the risk of GSD in carriers of the *ABCG8* variant, possibly harmful NSVs of the *ABCB4* gene, which reduce its activity as a translocator of phospholipids from hepatocytes to bile, which are involved in the formation of vesicles and the solubilization of cholesterol in bile (Fig.) [53].

Limitations

This article is not a systematic review. The advantage of the article is that it considers the latest available publications on the function of ABCG5 and ABCG8 sterol transporters, their effect on lipid metabolism, and the important role of the rs11887534 NSV of the *ABCG8* gene in GSD in children and adults and in GBC. Until now, not a single study has been published in Russia on the prevalence of the NSV of the *ABCG5* and *ABCG8* genes in GSD and GBC, as well as their clinical aspects, as well as the NSV of other genes and factors mediating the effects of these genes.

Conclusion

The causes of GSD are complex genetic and environmental factors, the prevalence of GSD in the world is growing due to the obesity epidemic, which is associated with hyperlipidemia and metabolic syndrome. Transport protein ABCG5/G8 plays a key role in hepatic secretion and intestinal absorption of cholesterol: one of the main genetic risk factors for GSD, the D19H variant of the *ABCG8* gene

(rs11887534), is associated with a 3.2-fold increase in transporter activity, which leads to bile supersaturation with cholesterol and a 2-fold increase in the risk of GSD in adults and a 4-fold increase in children. The presence of the D19H H allele is associated with a two-fold risk of recurrence of GSD after cholecystectomy [29]. ABCG5/G8 has been identified as the *LITH9* gallstone gene in the pathogenesis of GSD in humans. Since bile supersaturation with cholesterol in rs11887534 carriers manifests itself already in childhood, these genetic defects should be identified as early as possible for primary prevention of GSD, possibly using gene therapy.

Therefore, the ABCG5/G8-dependent pathway, which plays an important role in the formation of cholesterol gallstones, may be a potential therapeutic target in GSD, as well as in preventive medicine, which will help to significantly reduce the risk of GSD and GBC, since gallstones are the strongest predictor of GBC.

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