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REVIEW ARTICLE

Cancer predisposition in diabetics: risk factors considered for predictive diagnostics and targeted preventive measures

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Abstract *Diabetes mellitus* (DM) is a lifelong progressive disease with high morbidity and mortality worldwide. Whereas cardiovascular complications are well-known for DM, increasing evidence indicates that diabetics are predisposed to cancer. Understanding of molecular pathomechanisms of cancer in DM is of great importance. Dysregulation of glucose/insulin homeostasis leads to increased production of Reactive Oxygen/Nitrogen Species (ROS/RNS) and consequent damage to chromosomal/mitochondrial DNA, a frequent finding in DM. Long-term accumulation of modified/damaged DNA is well-acknowledged as triggering cancer. DNA-repair is a highly energy consuming process provoking increased mitochondrial activity. Particularly dangerous is a provoked activity of damaged mitochondria leading to a "vicious circle" lowering energy supply and potentiating ROS/RNS production. Mitochondrial dysfunction may be implicated in pathomechanisms of diabetes-related cancer. High risk for infectious disorders and induced viral proto-oncogenic activity may further contribute to cancer provocation. Much attention should be focused on preventive measures in diabetic healthcare, in order to restrict severe diabetes-related complications.

Keywords Cancer in diabetes · Prognostic risk factors · Preventive diagnostics · Targeted preventive measures · Stress/viral etiology · Advanced technologies

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Diabetes mellitus as general risk factor for cancer

Diabetes mellitus (DM) is a group of metabolic disorders, mainly characterized by impaired glucose metabolism and consequent hyperglycemia as the common feature. Whereas cardiovascular complications are well described for DM [1], it is a relatively new consideration that diabetic patients are highly predisposed to cancer. In spite of some ethnic-, gender-, and age-specific differences, significantly increased risk of liver, pancreas, bladder and digestive tract cancer types is generally recognized for DM-patients (Fig. 1).

Many population studies indicate an increased risk for almost all kinds of cancer in DM with particular ethnic- as well as gender-dependent preferences (Fig. 2).

With respect to single DM-types, population studies have been carried out in different countries showing geographic particularities in cancer incidence. Thus, long-term monitoring of a cancer-specific incidence in the subpopulation of type 1 diabetics was performed in Sweden during 1965–1999 [8]. It is noteworthy that particular risk in childhood was demonstrated for endometrial, buccal-cavity, bladder as well as cervix cancer types (Fig. 3). In adulthood, the highest risk has been registered for cancer of stomach, endometrium, cervix, and bladder.

Similar studies carried out for type 2 diabetes demonstrate liver, pancreas and bladder cancer to be the leading types (Fig. 4).

Cancer-related mortality in diabetics

According to the current worldwide statistics, every 10 s one patient dies due to DM-related consequences: DM is currently the fourth leading cause of death [10]. Furthermore, accumulating data demonstrate that, once appeared, cancer

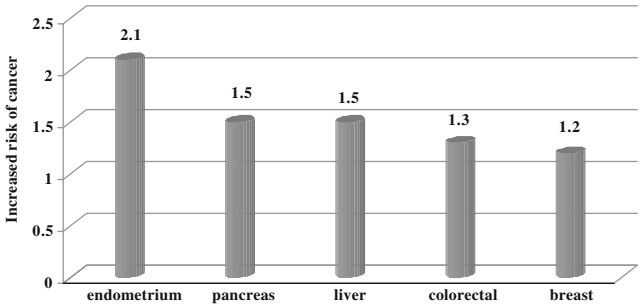

Fig. 1 General predisposition of diabetics to single cancer types: breast [2], endometrial [3], colorectal [4], pancreas [5], and liver [6] cancers

outcomes have worse prognosis for diabetics compared to non-diabetic oncologic patients (Fig. 5).

This general figures are well-supported by data collected in USA to treatment of single cancer types as represented in Fig. 6. These data clearly indicate less success in treatment of cancer for DM-patients.

The hindered treatment of oncologic diseases in diabetes care is, however, not the only reason of significantly increased cancer-related mortality of diabetics. Recent studies indicate that diabetics are generally predisposed to cancer development [2–9, 11–22]. Here we overview subcellular and molecular mechanisms that can contribute to cancer-provocation in diabetics.

Subcellular and molecular mechanisms in DM-predisposition to cancer

Mitochondrial dysfunction

Increased oxidative stress has been implicated in molecular pathomechanisms of DM and majority of chronic diseases developed secondary to diabetes [23–25]. Several studies demonstrated the excessive production of ROS to be the common feature of both diabetes types [10, 22, 26–28]. Disturbed glucose/insulin homeostasis initiates overall cellular stress leading to ir/reversible damage to subcellular structures [28, 29].

Oxidative damage to DNA is well documented for cells isolated from diabetics [30]. These findings indicate an imbalance between the increased production of ROS and decreased DNA-repair capacity. Depending on a quality of cell-cycle controlling machinery, this imbalance can lead either to extensive apoptotic cell lost or proliferation of damaged cells [31]. Whereas the first process causes mainly tissue-degeneration, the latter predisposes to cancer development. Both degenerative alterations in damaged organs and predisposition to cancer have been reported for DM-patients.

Extensive damage to DNA as well as mutations has been demonstrated also for mitochondria in DM-patients [28, 32, 33]. Mitochondrial genetic background as well as mitochondrial stress-response is considered as an important contributor in predisposition to cancer in diabetics [32, 34, 35]. Electron transfer chain (ETC) is the main energy source essential for performance of all cellular functions. Particularly, DNA-repair is a highly energy-consuming machinery, the efficiency of which obligatory depends on the quality of mitochondria. Mitochondrial DNA variations may affect a highly sensitive balance between ETC-efficiency and production of ROS in favor of the latter increasing, therefore, mutagenic effects of ROS and decreasing energy production. This is so called "vicious circle" resulting in mitochondrial dysfunction (Fig. 7). As for mitochondrial protein repertoire, both quantitative and qualitative changes in ND1-ND6 (NADH-dehydrogenases

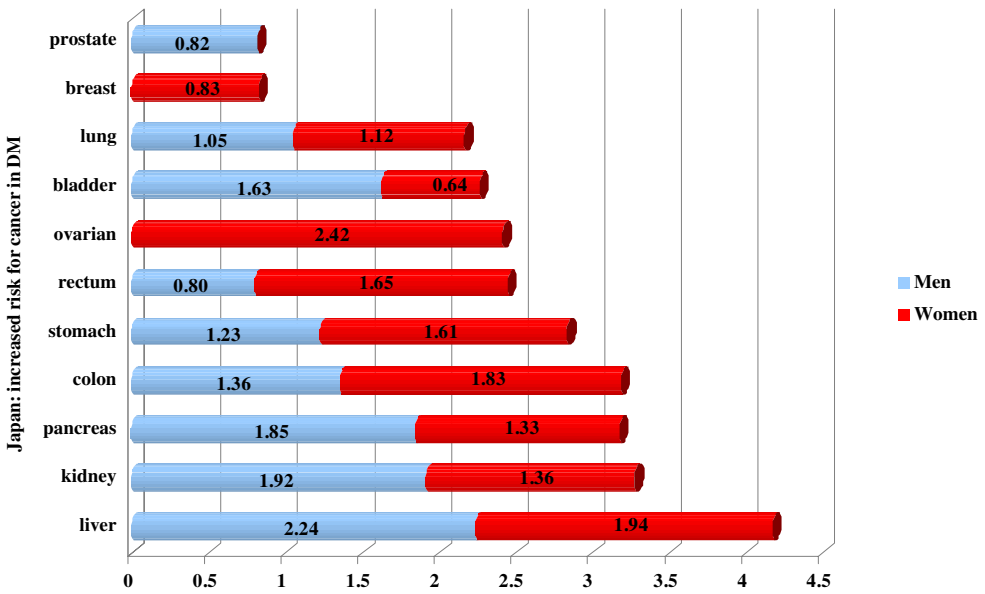

Fig. 2 Population studies in Japan as an example of cancer predisposition of diabetics in years 1990–2003 [7]

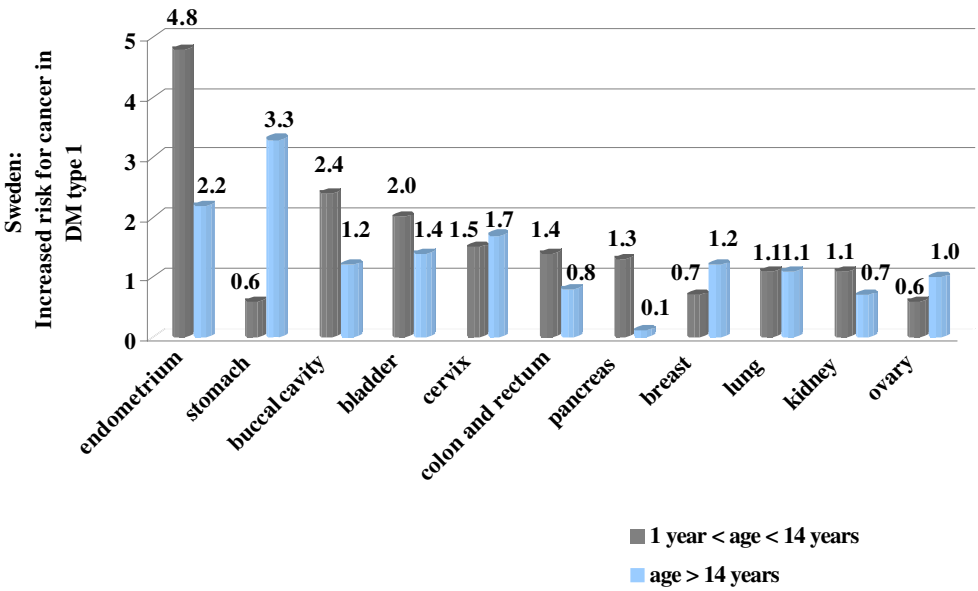

Fig. 3 Specific cancer incidence with respect to age in Swedish diabetics type 1 registered in years 1965–1999 [8]

of the ETC-complex I) have been shown to contribute to the "vicious circle" resulting in premature aging and plenty of pathologies including neurodegeneration and cancer [36]. In diabetics, the mitochondrial "vicious circle" has been implicated specifically in individual predisposition to breast cancer [37].

Concept of viral etiology in DM-provoked cancer

Patients with diabetic history are at increased risk of infection [38–40]. There is a growing body of evidence for compromised immune response in this patient cohort as a consequence of metabolic syndrome [41–43]. This imbalance can lead to highly increased incidence of viral infection potentiating cancer risk in diabetics [43–46].

Currently it is already well-acknowledged that more than 15 % of viral infections are able to cause cancer in humans [47]. Thus, human papillomavirus (HPV) infection is attributed to 80 % of all human cancers and was proposed to play a central role in molecular pathomechanisms of breast cancer [48–50]. Integration of viral particles in human genome frequently results in activation of several proto-oncogenes, which in turn trigger tumorigenic mechanisms in affected cells [22, 48, 51–53]. Thus, a viral activation of proto-oncogene c-MYC is well described in literature [48]. Thereby, a targeted integration of viral particles in human genome plays the crucial role for consequent cancer development [47, 48, 54]. In this context, HPV demonstrates clear preference for its integration sites, mainly in regions situated closely to c-MYC

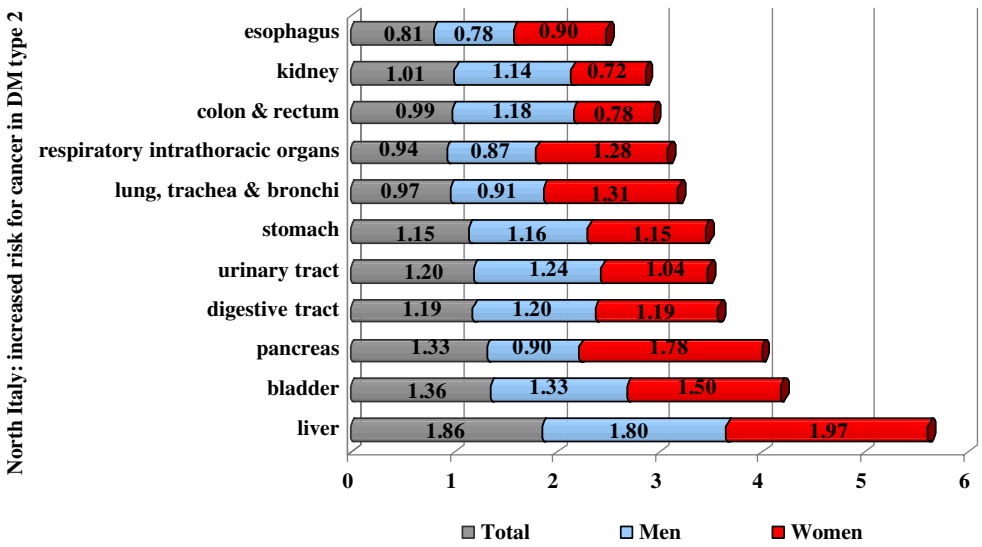

Fig. 4 Cancer risk for type 2 diabetics in North Italy in years 1987–1996 [9]

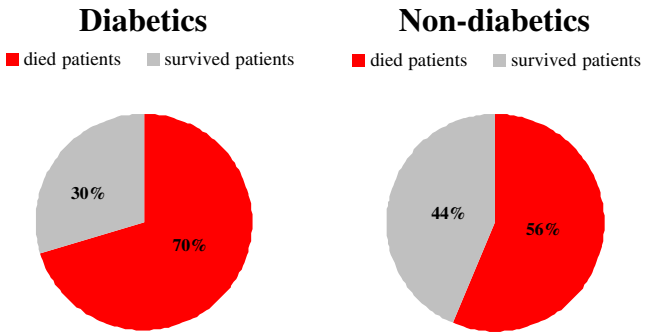

Fig. 5 Mortality by cancer in diabetic *versus* non-diabetic patients registered in Netherlands in years 1995–2002 [11]

coding sequences [48]. Once activated, c-MYC protein suppresses the cell-cycle controlling activity of P53, and allows, therefore, the development of new tumorigenic phenotype of transformed human cells [22, 48, 52]. In consensus, the activated synthesis of viral proteins E6, E7, E1 and E2 has been shown to be involved in cancer-related cell transformation [48, 55]. Most relevant mechanisms for viral etiology of cancer predisposition, particularly, in DM-pathology are summarized in Fig. 8.

The overall concept of cancer-predisposition in diabetics

Taking together the above given facts, we conclude that diabetics may be highly predisposed to cancer development specifically due to following contributors [57]:

- strong stress factors (excessive metabolic alterations, disturbed glucose/insulin homeostasis, hormonal de-regulation, insufficient detoxification) with consequently excessive production of ROS
- mitochondrial dysfunction with consequent low energy production, insufficient repair capacity and accumulating damage to both chromosomal and mitochondrial DNA
- high risk for infectious disorders with consequently induced viral proto-oncogenic activity as well as activity of particular pathogenic bacterial forms such as *Helicobacter pylori*.

Adequacy of stress response, repair capacity as well as immune defence are highly individual for each patient and strongly depend on risk factors such as genetic background, age, environmental factors, nutrition, body culture, life style, etc. (Fig. 9). Thus, varying breast cancer risk in different ethnic and social groups is well documented [16, 58–60]. Breast fat deposits and distribution increase risk for breast cancer in female and even in male patients [16, 61–65]. In contrast, breast cancer development is significantly reduced in people with regular physical activity [66]. Alcohol abuse and tobacco consumption are further contributors which remarkably increase risk of cancer development [17, 20, 67–71].

Outlook

Current biotechnology possesses sufficient power to estimate the severity of damage to subcellular structures, individual stress reactions and repair capacity. For example, by stress proteome profiling in peripheral leukocytes and blood plasma, individual stress reactions can be well estimated. Advanced predictive diagnostic approaches are currently close to clinical application and allow to select groups of risk and to estimate a

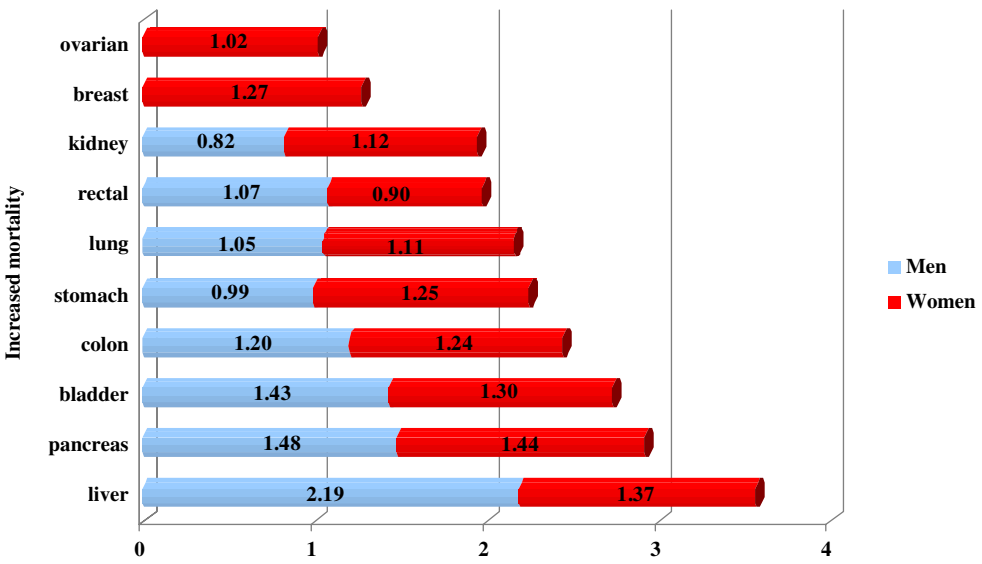

Fig. 6 Increased mortality of diabetics *versus* non-diabetics for single cancer types as documented for patients treated in USA in years 1982–1998 [12]

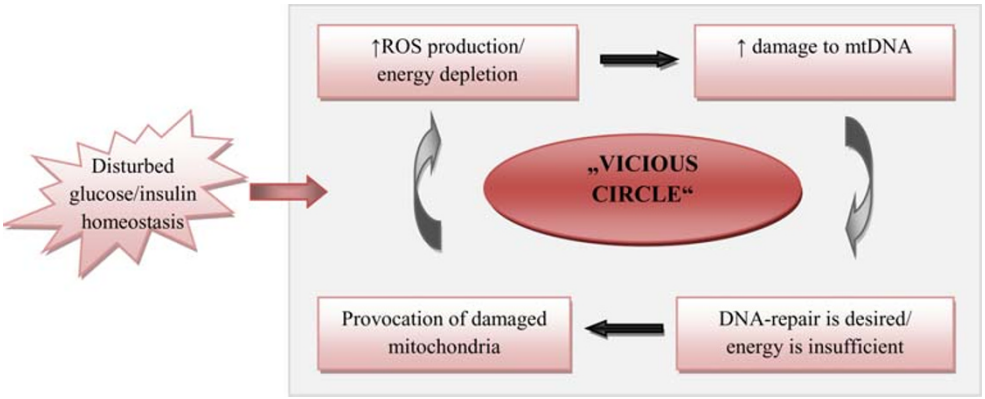

Fig. 7 Mitochondrial "vicious circle" causes a dangerous imbalance between highly increased production of ROS on one side and low energy production on the other side. Highly increased damage to chrDNA and mtDNA, remarkably decrease repair capacity as well as compromise cell-cycle control are direct consequences of stress-provoked mitochondrial dysfunction [22, 26, 28, 33, 36]

predisposition to severe complications in diabetics [34, 82–84].

Much attention should be focused on preventive measures in diabetic healthcare, in order to restrict or even avoid severe secondary complications, such as cancer [85]. Potential groups of risk should be informed about good lifestyle choices. Nowadays, it is increasingly clear that a well-balanced individually created diet is considered as an effective preventive measure and treatment of majority of chronic complications in diabetics [86–88].

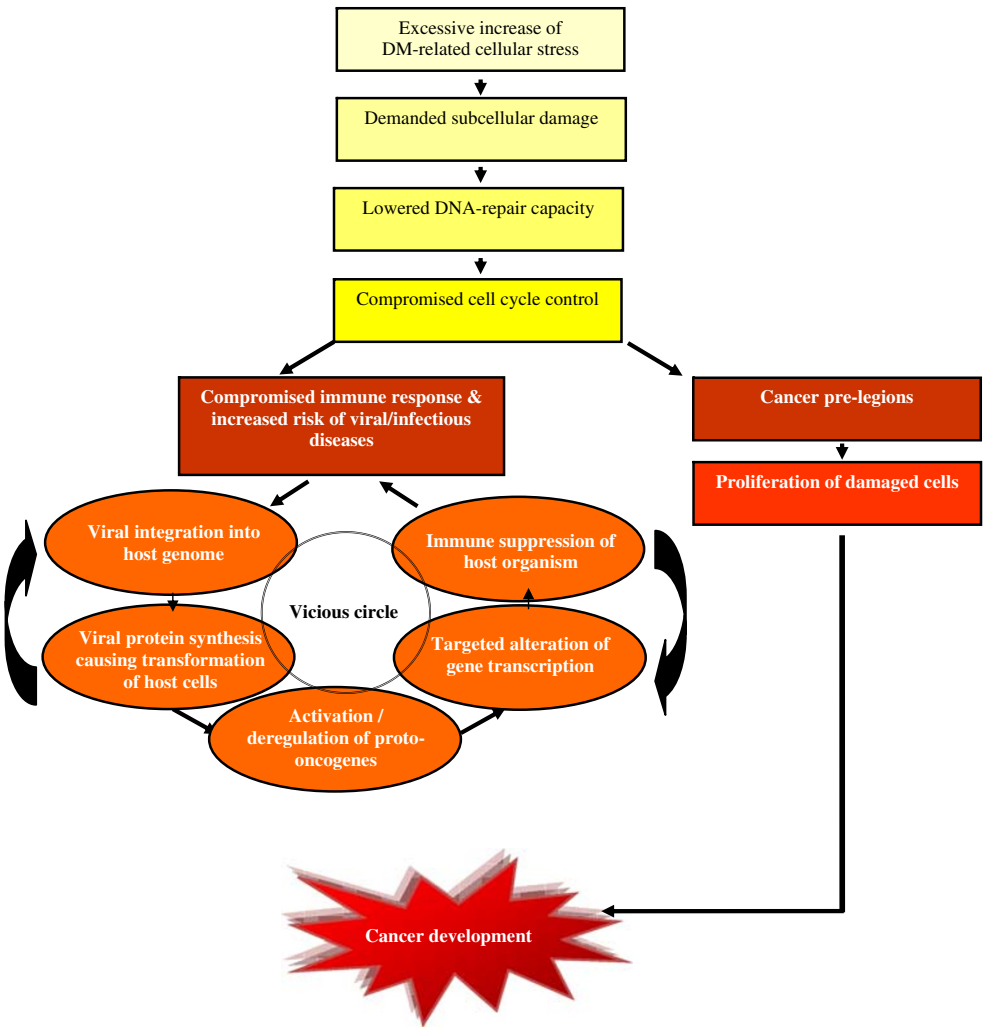

Fig. 8 Clue to viral etiology in DM-provoked cancer: "vicious circle" is the particularity of metabolic syndrome with high risk of cancer development [22, 26, 28, 33, 36, 38–45, 51–56]

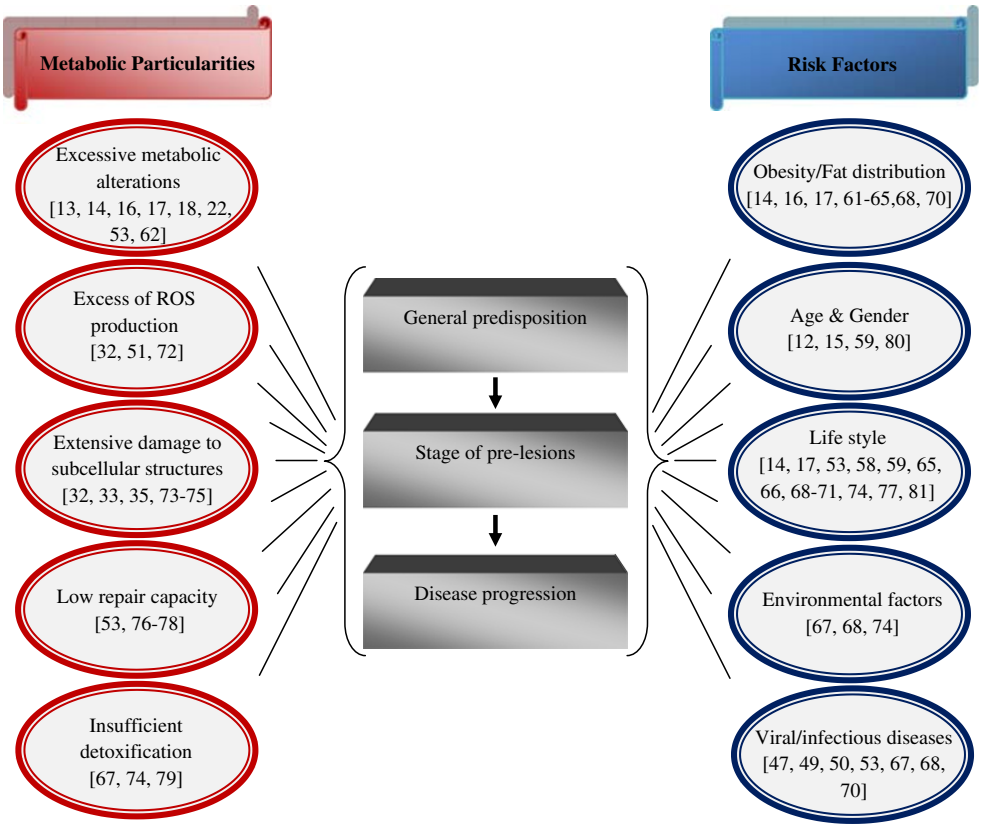

Fig. 9 Particularities of metabolic syndrome and factors contributing to cancer development. Corresponding references are given

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