Original Article

Genetic predisposition and prediction protocol for epithelial neoplasms in disease-free individuals: A systematic review

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Abstract

Background: Epithelial neoplasm is an important global health-care problem, with high morbidity and mortality rates. Early diagnosis and appropriate treatment are essential for increased life survival. Prediction of occurrence of malignancy in a disease-free individual by any means will be a great breakthrough for healthy living.

Aims and Objectives: The aims and objectives were to predict the genetic predisposition and propose a prediction protocol for epithelial malignancy of various systems in our body, in a disease-free individual.

Methods: We have searched databases both manually and electronically, published in English language in Cochrane group, Google search, MEDLINE and PubMed from 2000 to 2019. We have included all the published, peer-reviewed, narrative reviews; randomized controlled trials; case–control studies; and cohort studies and excluded the abstract-only articles and duplicates. Specific words such as "etiological factors," "pathology and mutations," "signs and symptoms," "genetics and IHC marker," and "treatment outcome" were used for the search. A total of 1032 citations were taken, and only 141 citations met the inclusion criteria and were analyzed.

Results: After analyzing various articles, the etiological factors, clinical signs and symptoms, genes and the pathology involved and the commonly used blood and tissue markers were analyzed. A basic investigation strategy using immunohistochemistry markers was established.

Conclusion: The set of proposed biomarkers should be studied in future to predict genetic predisposition in disease-free individuals.

Keywords: Basic investigation, biomarker, blood markers, disease-free individual, epithelial neoplasm, genetic predisposition, immunohistochemical marker

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INTRODUCTION

Epithelial neoplasm is an important global health-care problem, with high morbidity and mortality rates.[1] Cancer is a polygenic disease which shows several epigenetic factors influenced by genetic predisposition with resultant DNA damage and genomic instability. The clinical diagnosis of any epithelial malignancies depends on the signs and symptoms related to the organs affected.[2,3] The

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histopathology remains the gold standard in diagnosing the disease, but immunohistochemistry is also required not only for diagnosis but also for treatment in case of undifferentiated tumors. Moreover, the overall survival rate is contingent upon staging and grading of the tumor.[5-7] Diagnosing at an advanced stage of the disease makes the removal of tumors difficult and therefore, early detection methods and prevention strategies are essential to reduce cancer mortality.

The American Society of Clinical Oncology recommends genetic counseling and testing in the setting of pre- and post-test counseling, which should include the discussion of possible risks and benefits of early detection of malignancies and prevention modalities.[5,7] Carriers of mutations may be detected through laboratory analysis of the genetic structure of the blood and the tissue with the assistance of biomarkers.

None of the cancer susceptibility tests currently available is as yet appropriate for screening of asymptomatic individuals, however identification of a mutation in an affected member of the family may influence medical management and can be used as a critical baseline in the testing of other family members.[8,9] Thus, the aim of this review is to analyze and summarize the results of published studies and to identify and introduce an investigation protocol for epithelial malignancies using feasible molecular markers in a disease-free individual to predict genetic predisposition.

MATERIALS AND METHODS

This systematic review was conducted in harmony with Preferred Reporting Items for Systematic reviews and Meta-Analyses Statement Criteria (Moher, Liberati, Tetzlaff, Altamn and PRISMA Group, 2010) [Figure 1].

Inclusion criteria

In this review, we included the full papers; English literature which were published after 2000; all peer-reviewed articles; observational studies such as cohort, case–control and retrospective studies; and all the articles which used both tissue and blood as a source of biomarkers for the diagnosis and prognosis of various epithelial neoplasms. We included those articles which used blood biomarker to predict the epithelial neoplasm.

Exclusion criteria

All the duplicates and abstract-only articles were excluded. Articles which used markers only to diagnose epithelial neoplasm were also excluded.

Sources, search strategy and study selection

Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE) on Cochrane Library and Centre for Reviews and Dissemination (CRD), EMBASE, MEDLINE, SCI-EXPANDED, PUBMED and PUBMED CENTRAL were searched to identify the records pertaining to this review.

The search strategy is summarized in Table 1. The eligibility of this study was individually assessed in an unblinded manner by two reviewers. In the first phase of this review, all the databases were screened by the title and abstract; in the second phase, each article was read fully by each other. If discrepancies were found, they were corrected by another observer, if any.

Data extraction and management

The data which were included in this review such as etiological factors, clinical signs and symptoms, diagnostic criteria, genetic predisposition, blood biomarkers, prognostic markers and immunohistochemical tissue markers were checked and reviewed by the authors. The observations were extrapolated and entered on a customized data collection format, which were tabulated in Tables 2-4. The collected data were independently analyzed by each author.

Table 1: Systematic review search strategy for PubMed, Embase and Cochrane

Database	Keyword and search method
PubMed	Epithelial neoplasm AND etiologic factors
	Epithelial neoplasm AND clinical feature
	Epithelial neoplasm AND genetic predisposition
	Epithelial neoplasm AND biomarkers
	Epithelial neoplasm AND blood markers
	Pathology AND genes involved
Embase	Head and neck cancer AND blood markers
	Lung cancer AND blood markers
	Breast cancer AND blood markers
	Colorectal cancer AND blood markers
	Cancer of female reproductive tract AND blood markers
	Cancer of male reproductive tract AND blood markers
	Thyroid cancer AND blood markers
	Pancreas cancer and blood markers
	Head and neck cancer AND tissue markers
	Lung cancer AND tissue markers
	Breast cancer AND tissue markers
	Colorectal cancer AND tissue markers
	Cancer of female reproductive tract AND tissue markers
	Caner of male reproductive tract AND tissue markers
	Thyroid cancer AND tissue markers
	Pancreas cancer and tissue markers
Cochrane	Head and neck cancer AND genetic predisposition
	Lung cancer AND genetic predisposition
	Breast cancer AND genetic predisposition
	Colorectal cancer AND genetic predisposition
	Cancer of female reproductive tract AND genetic predisposition
	Cancer of male reproductive tract AND genetic predisposition
	Thyroid cancer AND genetic predisposition
	Pancreas cancer and genetic predisposition

Table 2: Etiological factors and clinical signs and symptoms

Criteria	Head-and-neck cancer	Colorectal cancer	Breast cancer	Liver cancer	Bladder cancer	Pancreatic cancer	Cancer of female reproductive tract: cervical, uterine, ovarian	Cancer of male reproductive organ: prostrate testis	Lung cancer	Thyroid cancer	Gatrointestinal cancer	Skin cancer
Author details	Saleh K, Joshi P, Dutta, Shaw R, Perdomo S, Macfarlane T V, Omar EA	Rosa M De, Boelens PG, Granadosro, Mero JJ	Buechler SA, Ye Z, Wang C, Mansfield CM Sharifi J, Chen W,	Mohammadian M, Waller LP, Badvie S. Sia D,	Edmondson AJ, Pasin E, Barbosa LA, Metts MC, Soubra A, Shephard EA	Malhotra L, Be C, Earl F, Mcguigan A, Factors R, Darmawan G	Moscicki A, Ramesh N, Cline JM. Wentzensen N, Hedayatizadeh-omran A, Herbst L. markers, Flake GP Weiderpass E	Tvrda E, John R.Giudicessi	Factors R, Cooley ME. Holgate ST, Ganie F Latimer KM,	Nguyen QT,	Management C. Yusefi AR,	Factors R, Patients FOR. Bax MJ, Johnson TM, Rastrelli M, Das P Melanoma C, Cancer S, Found B
Etiological factors	HPV Fungal infection Sharp teeth Family history Smoking, diabetes, alcohol consumption, obesity, decreased physical activity, decrease in fruit and vegetable consumption, decrease in the consumption of dairy products, decrease in the consumption of folate, fibers and Vitamin D	Red meat consumption Processed food NSAIDS Family history Smoking, diabetes, alcohol consumption, obesity, decreased physical activity, decrease in fruit and vegetable consumption, decrease in the consumption of dairy products, decrease in the consumption of folate, fibers and Vitamin D	Hormonal factors Young-age menarche Regular/ irregular menstrual cycle Older age menopause Oral contraceptives Family history, smoking, diabetes, alcohol consumption, obesity, decreased physical activity, decrease in fruit and vegetable consumption, decrease in the consumption of dairy products, decrease in the consumption of folate, fibers and Vitamin D	Chronic hepatitis with advanced fibrosis/cirrhosis Hereditary hemochromatosis Alpha-1 antitrypsin deficiency Porphyria's Fatty liver disease Wilson's disease Glycogen storage disease Tyrosinemia type I Hereditary telangiectasia Hypercitruelimia Aflatoxin exposure Polyvinyl chloride Carbon chloride Family history Smoking, diabetes, alcohol consumption, obesity, decreased physical activity, decrease in fruits and vegetable consumption, decrease in the consumption of dairy products, decrease in the consumption of folate, fibers and Vitamin D	Cooking in fumed wood Industrial carcinogen: aromatic amines, azodyes Gasoline exhaust Methenamine vapor Drugs: cyclophosphamide, chloromethane, phenacetin, nitrosamines Chlorinated water Hair dyes Saccharine's HSV infection Family history Smoking, diabetes, alcohol consumption, obesity, decreased physical activity, decrease in fruit and vegetable consumption, decrease in the consumption of dairy products, decrease in the consumption of folate, fibers and Vitamin D	Exposure to pollutants Chronic pancreatitis disease Gall stones Pylori Family history Smoking, diabetes, alcohol consumption, obesity, decreased physical activity, decrease in fruit and vegetable consumption, decrease in the consumption of dairy products, decrease in the consumption of folate, fibers and Vitamin D	HPV HSV Family history, smoking, diabetes, alcohol consumption, obesity, decreased physical activity, decrease in fruit and vegetable consumption, decrease in the consumption of dairy products, decrease in the consumption of folate, fibers and Vitamin D	Selenium Androgens Vasectomy Family history Smoking, diabetes, alcohol consumption, obesity, decreased physical activity, decrease in fruit and vegetable consumption, decrease in the consumption of dairy products, decrease in the consumption of folate, fibers and Vitamin D	Air pollution Radon gas Asbestos Family history Smoking, diabetes, alcohol consumption, obesity, decreased physical activity, decrease in fruit and vegetable consumption, decrease in the consumption of dairy products, decrease in the consumption of folate, fibers and Vitamin D	X-rays Radioactive iodine Hypo- and hyper-thyroidism Family history Smoking, diabetes, alcohol consumption, obesity, decreased physical activity, decrease in fruit and vegetable consumption, decrease in the consumption of dairy products, decrease in the consumption of folate, fibers and Vitamin D	HPV Pylori HPV 16 and 18 Acid and bile reflux Increase in salt intake Polyaromatic hydrocarbons Family history Smoking, diabetes, alcohol consumption, obesity, decreased physical activity, decrease in fruit and vegetable consumption, decrease in the consumption of dairy products, decrease in the consumption of folate, fibers and Vitamin D	Serious blistering sun burns UV radiation Family history Smoking, diabetes, alcohol consumption, obesity, decreased physical activity, decrease in fruit and vegetable consumption, decrease in the consumption of dairy products, decrease in the consumption of folate, fibers and Vitamin D

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Table 2: Contd...

Criteria	Head-and-neck cancer	Colorectal cancer	Breast cancer	Liver cancer	Bladder cancer	Pancreatic cancer	Cancer of female reproductive tract: cervical, uterine, ovarian	Cancer of male reproductive organ: prostrate testis	Lung cancer	Thyroid cancer	Gatrointestinal cancer	Skin cancer
Clinical signs and symptoms	Red/whitish patch Ulcero proliferative growth, Lump/mass without pain Hoarseness Frequent epistaxis Difficulty in breathing Double vision Difficulty in chewing/swallowing	Polyp- inner lining of the colon/rectum Bleeding from the rectum Blood in stool after the bowel movement Cramping in the lower abdomen Urge for bowel emptying Constipation and diarrhea last for few days Decrease in appetite Weight loss	Lump in the breast Painful Nipple Nipple discharge: blood discharge	Hepatitis/cirrhosis Large tumors may cause abdominal pain Malaise Weight loss Fatigue Fullness Jaundice Paraneoplastic syndrome Hypercalcemia Hormonal imbalance GIT/esophageal bleeding	Hematuria Changes in the bladder habit Urinate more often Pain during urination Bladder fullness Weak urine stream Unable to urinate Lower back ache Swelling in the feet	Nausea Vomiting Bloating Steatorrhea Abdominal pain Weight loss Jaundice Ascites Gastrointestinal bleeding Hepatomegaly	Back pain Edema in the lower extremity Uterine bleeding Irregular postmenopausal bleeding Dysuria Bloating	Difficulty in urinating Prostrate hypertrophy Back pain Hemoptysis Gynecomastia	Fatigue Labored breathing Persistent cough Decreased appetite Hoarseness of voice Wheeze, Stridor pneumonia	Nodule single/multiple Dyspepsia Dyspnea Hoarseness Cervical lymphadenopathy	Nausea Vomiting Bleeding Ulcer Weight loss Steatorrhea Abdominal pain Bloating Dysphagia Dyspepsia	Irregularity of the mole Blurred/ragged edges Alteration in the pigmentation Increase in the size and shape of the mole Itching/tenderness of the mole Pain and Swelling of the lymph nodes
Diagnosis	Stage I	Stage I	Stage I	Stages II and III	Stage I	Stages III and IV	Stages I and II	Stages I and II	Stages I and II	Stages I and II	Stage I	Stages I and II

HPV: Human papillomavirus, HSV: Herpes simplex virus, NSAIDS: Nonsteroidal anti-inflammatory drugs, UV: Ultraviolet, Pylori: *Helicobacter Pylori*, GIT: Gastrointestinal tract

Table 3: Genes and pathology involved in various epithelial neoplasms

Tumor	Author details	Pathology	Genes involved
Head-and-neck cancer	Major AG, Mehrotra R, Hoffmann F, Suh Y, Jou A, Patil DB, Owusu-afriyie O, Yi C, Dahiya K, Negi M	TP 53 Rb 17 LOH	*P16* *9pLOH*
Colorectal cancer	Soyano AE, Kanik P	APC -5q21-22 Mismatch MSH 2, MSH3, MLH1 PMS 1 MSH 6	P16 P15 BUB 1 Cyclin D1 MMP E-cadherin CD44
Breast cancer	Hou L, Myp C, Sporikova Z	LOH at multi loci BRCA1 BRCA 2 Estrogen receptor - positive P53 mutation Heterozygosity ATM P53 cerbB2 BCL	Ki67 MIB 1 Topoisomerase histone H3 TGF alpha, beta EGF P53 Caspases surviving P21 CD31,44, VGEF Brca1
Liver cancer	Daher S	Adenomatous hyperplasia Alpha-fetoprotein	Aflatoxin B1 P53 Cyclin D KRAS Beta-catenin
Bladder cancer	Soubra A, Xiao X, Koyuncuer A, Weyerer V, Ogawa O, Inamura K, Ifeanyi OE	Mutation - NAT2 gene GSTM - detoxification ERBB 2 Partial loss of chromosome 9 P16 P15 P53	9- LOH Cyclin D VGEF P53 RB PDECGF
Pancreatic cancer	Duffy MJ, Goonesekere NCW, Zapata M, Smith RA, Loosen SH, Hamada S, Malati T	BRCA2 P16 STK1 LKB1 Mutation of trypsinogen gene - 7q35	KRAS MYB AKT2 AIB1 ERBB2 P16 P53 DPC4 BRCA2 MKK4 MAH 2 MLH1
Gastrointestinal cancer	Pietrantonio F, Matthews LHM, Wang C, Tan C, Visser E, Wang YI	CAG gene mutation E-cadherin mutation LOH 1q3p, 5q, 6q, 7q, 9p, 17p P53 AT CG mutation Cyclin D HST1 HST2 EGFR Myc-polymorphism	KRAS C-MET C-ERBB2 CYCLIN D APC P53 Cadherin and cantenin CD44 translocation P53 APC FHIT CDKN2A CD95 FAS EGFR C-ERBB2 UPA KI67 RAB1

Contd...

Table 3: Contd..

Tumor	Author details	Pathology	Genes involved
Skin cancer	Weinstein D, An I, Harman M, Lim SY, He T, Soumya D	Loss of function of melanocortin receptor 1 Cdkn2a mutation P16 CDK 4 CDKN2 PTEN-1p, 6q, 7p, 11q P53 Myc BRAF	CDK1 MC 1P P53 MYC
Cancer of female reproductive tract: cervical, uterine, ovarian	Dong X, Prat J, Wang T Rein BJD	CIN 1,2,3,4 Diploid/polypoid associated with HPV c-myc N-MYC KRAS FHIT CYT P141 C-ERBB2 PTEN LOH 3P	HPV FHIT P53 KRAS MYC LOH-3P PTEN BRCA P16 Cyclin D1 E-cadherin CD44
Cancer of male reproductive organ: Prostrate testis	Nagirnaja L, Achermann JC	P53 BCL2 Mutation IN X chromosome 1P Iscero 12P Cyclin D	LOSS of 8P21 NKX 3.1 10Q 13Qrb P53
Lung cancer	Inamura K Cheng L, Travis WD	Polymorphism of cytochrome p450 gene P 53 mutation Point mutation-KRAS FHIT (fragile histidine triad) 3p 14.2-preneoplastic lesion Homozygous deletion and silencing methylation in CDK inhibitors p16ink	P53 KRAS CDKN2a P16 LOH 3p FHIT
Thyroid cancer	Thapa J Abdullah MI, Nosé V Li X, He J	MEN type 2A RET proto-oncogene Mutation of PTC 1, 2, 3	TSH RAS LOH 3P PAX 8 PTEN P53 RET/PTC TRK BRAF MFT

TP 53: Tumor suppressor gene, LOH: Loss of heterozygosity, P16: Cyclin-dependent kinase inhibitor 2A, APC: Adenomatous polyposis coli, MSH: Mut S protein homolog, MLH-1: Mut L protein homolog 1, PMS 1: Protein homolog 1, BUB: Budding uninhibited by benzimidazole 1, MMP: Matrix metalloproteinases, P15: Multiple tumor suppressor gene, CD 44: Cell surface glycoprotein, cell-cell interactions, BRCA: Breast cancer gene, ATM: Ataxia-telangiectasia mutated, cerbB2: Receptor tyrosine-protein kinase erbB-2, BCL: B-cell lymphoma, ki67: Nuclear protein associated with cellular proliferation, MIB: E3 ubiquitin-protein ligase, TGF: Transforming growth factor, P21: Potent cyclin-dependent kinase inhibitor, CD 31: Platelet endothelial cell adhesion molecule, NAT: N-acetyltransferase, GSTM: Glutathione S-transferase Mu 1, KRAS: Kirsten rat sarcoma viral oncogene homolog, RB: Retinoblastoma, PDECGF: Thymidine phosphorylase, STK: Serine/threonine kinase family, LKB: Liver kinase B1, MYB: Myeloblastosis, AKT: Protein kinase B, AIB: Transcription factor ABA-inducible bHLH-TYPE, DPC4: Deleted in pancreatic cancer-4, MKK: Mitogen-activated protein kinase, MYC: Proto-oncogene BHLH transcription factor, HST: Human gene nomenclature, CDK: Cyclin-dependent kinase, CAG: Cytosine-adenine-guanine, C-MET: Tyrosine-protein kinase, CD 95: Apoptosis antigen 1, FAS: Cell surface death receptor, FHIT: Human accelerated region 10, UPA: Urokinase-type plasminogen activator-Ras-related in brain, BRAF: Raf murine sarcoma viral oncogene homolog B, PTEN: Phosphatase and tensin homolog, MEN: Multiple endocrine neoplasia type, RET: Rearranged during transfection, PAX: Paired box, TMFTRK: Tropomyosin receptor kinase A, MFT: phosphatidylethanolamine-binding protein

Risk of bias and quality assessment of studies

The quality and the nature of the article were reviewed by the authors using modified Ottawa scale. After completing the data extraction, it was evaluated by the third author.

RESULTS

Author details, etiological factors and clinical signs and symptoms of the various epithelial neoplasms are tabulated in Table 2.[11-149]

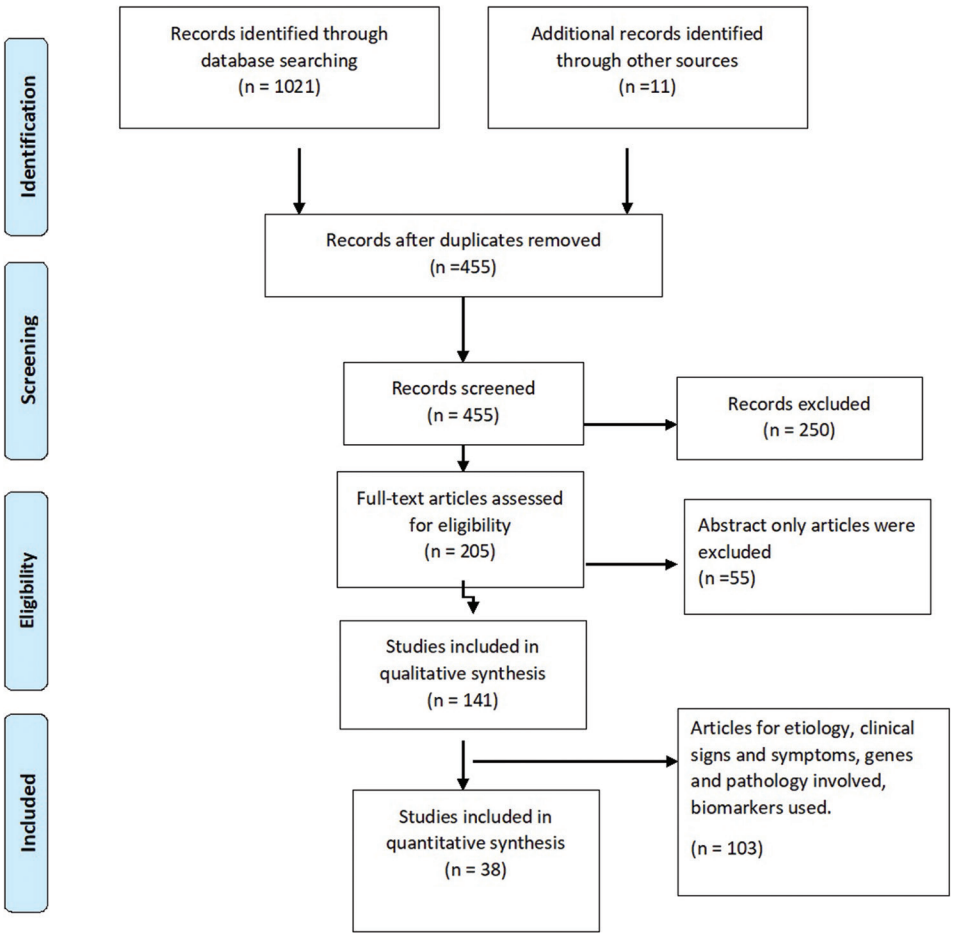

Figure 1: Flowchart for the systematic review

The genes and the pathology involved in the various epithelial neoplasms are tabulated in Table 3.[11-149]

The biomarkers used by authors for the various epithelial neoplasms are shown in Table 4.[11-149]

DISCUSSION

Cancer is a multistep process, which involves genetic and epigenetic factors responsible for its occurrence.[10] The etiopathogenesis of cancer can be divided into:[4]

1. Unmodifiable intrinsic risk which refers to inevitable spontaneous mutations (inherited) that arise as a result of DNA replication
2. Nonintrinsic risk which refers to:
   a. Modifiable exogenous/external factors (e.g., carcinogens, viruses and xenobiotic) and lifestyle factors (e.g., smoking, hormone therapy, nutrient intake and physical activity) that are exogenous to the host; and
   b. Endogenous factors that are partially modifiable and related to the characteristics of an individual (e.g., immune, metabolism, DNA damage response and hormone levels) and influence the key aspects of cell growth control and genome integrity.

The exposure to various epigenetic factors initially results in repairable DNA damage and upon continuous exposure to epigenetic factors and/or a genetic predisposition may lead to irreparable mutated cell and malignancy.[150] In this review, the etiology, clinical signs and symptoms, genes and the pathology involved and various tissue and blood markers of epithelial neoplasms were analyzed to arrive at an investigation protocol for disease-free individuals.

The analysis of the results of the study showed that though there are common etiological factors involved in the occurrence of various epithelial malignancies such as smoking, alcoholism and HPV, there are certain specific factors that influence the occurrence of malignancies in relation to a particular region or system involved. It was also observed that the usual clinical presentation of epithelial malignancies was a lump or ulceroproliferative

Table 4: Markers used by authors for various types of epithelial neoplasms

Author details	Markers	Type of specimen	Detection
Biaogeng *et al*.	CA 15-3 CEA	Serum	Breast cancer and its subtypes
Dorit laessig1 *et al*.	CA 15-3 CEA	Serum	Breast cancer and its subtypes
Alireza Abdullahi *et al*.	ER PR P53 HER 2	Tissue (IHC)	Breast cancer and its subtypes
Valentina Guarneri *et al*.	HER 2	Tissue (IHC)	Breast cancer and its subtypes
Grazia Carpino *et al*.	HER 2 HER 1	Tissue (IHC)	Breast cancer and its subtypes
Seyedabbasmirmalek *et al*.	HER 2 P53 Hormone receptor	Tissue (IHC)	Breast cancer and its subtypes
Michael j. Duffy	CA 15-3 BR 27.29 CEA TPA TPS HER-2	Serum	Breast cancer and its subtypes
Catherine e. Bond *et al*.	BRAF	Tissue	Colorectal cancer
Michael j. Duffy	CEA	Serum	Colorectal cancer
John h. Bond, MD	FOBT	Blood	Colorectal cancers
Alyssa M. Krasinski's	EGFR KRAS BRAF (genes) PIK3CA	Blood	Colorectal cancers
Gadepalli *et al*.	EGFR	Blood	Colorectal cancers
Chan dihedral	EGFR	Blood	Colorectal cancer
Jincheng *et al*.	ALK AND its inhibitor	Blood	Lung
Gilda da concha santos	EGFR	Blood and tissues (IHC)	Lung
Fernando c. Santini *et al*.	PD1	Blood and tissues (IHC)	Lung
D.Ed. Meyers *et al*.	PD-1/PD-L1 AXSIS	Blood	Lung
Oliver Dorigo *et al*.	CA125	Blood	Ovarian
T van Gore *et al*.	HE4 CA 125	Blood	Ovarian
John o. Scourge *et al*.	OPN	Blood	Ovarian
Lalita a. Shaved *et al*.	OPN	Blood	Ovarian
J. L. Humphries *et al*.	CA19.9	Serum	Pancreas
Ewe karna *et al*.	IGFR I IGF	Serum	Pancreas
R.talar-wojnarowska *et al*.	VEGF	Serum	Pancreas
Leonard s. Marks *et al*.	PCA3	Blood	Prostrate
Dragan Iliac *et al*.	PSA	Blood	Prostrate
Ji-fan lin *et al*.	MICRO RNA	Blood	Bladder cancer
Weige tan *et al*.	MICRO RNA25 P57	Blood	Gastric cancer
José marrugo *et al*.	Heat shock proteins	Blood	All cancers
Edward r. Sauter	Hormone receptor status CK HER2 Ki67 Oncotype Dx MammaPrint	Tissue	All cancer
Kiran Dahiya *et al*.	Chemokine receptor MMP HPV Interleukin MicroRNA MAGE Actin and myosin	Tissue/saliva	Head and cancer
Esam Ahmad Omar	ZEB1, ZEB2 KRAS PTEN P21 miRNA	Blood	Head and cancer

Contd...

Table 4: Contd...

Author details	Markers	Type of specimen	Detection
Saleh Daher *et al*.	miR-122 RASSF1A Histone-modifying genes	Blood	Liver cancer
Daniela Sia *et al*.	KRAS TP53 EGFR BRAF	Tissue/blood	Liver cancer
David Weinstein, md *et al*.	Melan-A, BUB1 and CD 63 RREB1 (6p25), MYB (6q23), Cep6 (Centromere 6), CDKN2A (9p21), RREB1 (6p25), MYC (8q24)	Tissue/blood	Melanoma
Su yin lim *et al*.	BRAF CXCL3 VEGF	Tissue/blood	Melanoma
Xiliangwang *et al*.	THCA TSHR TTF	Blood	Thyroid cancer
Buddhike Sri Harsha Indrasena	Thyroglobulin	Blood	Thyroid cancer

CA: Cancer antigen, CEA: Carcinoembryonic antigen, ER: Estrogen receptor, PR: Progesterone receptor, p53: Tumor suppressor, HER: Heregulin, TPA: Serum tissue polypeptide antigen, TPS: Tissue polypeptide-specific antigen, BRAF: Proto-oncogene B-Raf and v-Raf murine sarcoma viral oncogene homolog B, FOBT: The fecal occult blood test, EGFR: Epidermal growth factor receptor, KRAS: Kirsten rat sarcoma viral oncogene homolog, PIK3CA: Phosphatidylinositol 3-kinase, ALK: Anaplastic lymphoma kinase, PDL1: Programmed death-ligand 1, HE4: Human epididymis protein 4, OPN: Osteopontin, IGFR: Insulin-like growth factor receptor, VGEF: Vascular endothelial growth factor, MMP: Matrix metalloproteinase, MAGE: Tumor-specific antigen, ZEB: Zinc finger E-box binding homeobox, PTEN: Phosphatase and tensin homolog, BUB: Mitotic checkpoint protein, MYC: Basic helix-loop-helix protein, THCA: Tetrahydrocannabinol acid, TSHR: Thyroid-stimulating hormone receptor, TTR: Transthyretin, CA 15-3: Cancer antigen 15-3, UV: Ultraviolet

growth. However, depending on the region or system involved, the clinical signs and symptoms vary from one another. A derivation of the specific etiological factors and clinical signs and symptoms of various epithelial neoplasms is tabulated [Table 5]. Usually, the signs and symptoms occur as a precancerous lesion initially and upon continuous insult, it progresses to malignancy. The genetic predisposition definitely influences the potential role of epigenetic factors in the development of cancer by inducing mutations that result in changes from normal mucosa to various grades of dysplasia to malignancy.[151]

The lesions were able to be diagnosed clinically when it occurs in the oral cavity and cervical regions. However, lesions in other hidden areas were diagnosed using computed tomography, magnetic resonance imaging and endoscopic procedures. The authors have used histopathology as a gold standard method in diagnosing all the lesions and immunohistochemistry for diagnosing undifferentiated tumors as well as treatment planning. The authors have also used various markers in tissues and blood using different methods to diagnose the lesions. A derivation of the different tissue and blood markers used by various authors is tabulated [Table 6].

With the help of the above derivations, the most commonly used blood markers were analyzed and tabulated to arrive at a prediction protocol [Table 7]. This investigation protocol involving various biomarkers is proposed in this review to predict genetic predisposition and/or chances of occurrence of malignancy in a disease-free individual. We propose that the markers suggested should be tested in every individual with a strong family history or persons with strong association of various epigenetic etiological factors without the disease. Though the limitations of our proposal will be cost factor and lack of confirmatory evidence, this is the first kind of proposal given here to predict genetic predisposition in a disease-free individual.

CONCLUSION

This review summarizes the different aspects of the epithelial neoplasm of various systems of our body based on the literature published. It is clear that cancer is an urgent global challenge and needs a definite measure to scale up prevention, early detection and diagnosis, treatment and care services. The analysis of various articles reveals the basic pathology, its genetic involvement, etiology, clinical symptoms and various diagnostic modalities of the epithelial neoplasm of the body, which are essential for any individual who deals with diagnosis or treatment or research in the field of oncology. Thus, the markers identified following the analysis of scientific facts behind a cancer may be helpful in predicting the genetic predisposition in a disease-free individual. It should be studied in a large scale either system wise or organ specific wise in future to confirm its specificity and sensitivity.

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Nil.

Table 5: Specific etiological factors and clinical signs and symptoms of the epithelial neoplasms

Criteria	Head-and-neck cancer	Colorectal cancer	Breast cancer	Liver cancer	Bladder cancer	Pancreatic cancer	Cancer of female reproductive tract: cervical, uterine, ovarian	Cancer of male reproductive organ: prostrate testis	Lung cancer	Thyroid cancer	Gatrointestinal cancer	Skin cancer
Specific etiological factors	HPV Fungal infection Sharp teeth	Red meat consumption Processed food NSAIDS	Hormonal factors Young-age menarche Regular/irregular menstrual cycle Older-age menopause Oral contraceptives	Chronic hepatitis with advanced fibrosis/cirrhosis Hereditary hemochromatosis Alpha-1 antitrypsin deficiency Porphyria's Fatty liver disease Wilson's disease Glycogen storage disease Tyrosinemia type I Hereditary telangiectasia Hypercitruelimia Aflatoxin exposure Polyvinyl chloride Carbon chloride	Cooking in fumed wood Industrial carcinogen: aromatic amines, azodyes Gasoline exhaust Methenamine vapor Drugs: Cyclophosphamide, chloromethane, phenacetin, nitrosamines Chlorinated water Hair dyes Saccharine's HSV infection	Exposure to pollutants Chronic pancreatitis disease Gall stones Pylori	HPV HSV	Selenium Androgens Vasectomy	Air pollution Radon gas Asbestos	X rays Radioactive iodine Hypo- and hyper-thyroidism	HPV Pylori HPV 16 and 18 Acid and bile reflux Increase in salt intake Polyaromatic hydrocarbons	Serious blistering sun burns UV radiation
Specific clinical signs and symptoms	Red/whitish patch Ulcero proliferative growth, Lump/mass without pain Hoarseness	Bleeding from the rectum Blood in stool after the bowel movement Cramping in the lower abdomen	Lump in the breast Painful nipple and discharge	Hepatitis/cirrhosis Large tumors may cause abdominal pain Malaise Weight loss	Hematuria Changes in the bladder habit Urinate more often Pain during urination	Nausea Vomiting Bloating Steatorrhea	Back pain Edema in the lower extremity	Difficulty in urinating Prostrate hypertrophy	Labored breathing Persistent cough Decreased appetite Hoarseness of voice Wheeze, stridor	Nodule (single/multiple) Dyspepsia Dyspnea	Nausea Vomiting Bleeding Ulcer Dysphagia Dyspepsia	Irregularity of the mole Blurred/ragged edges Alteration in the pigmentation
Diagnosis	Stage I	Stage I	Stage I	Stages II and III	Stage I	Stages III and IV	Stages I and II	Stages I and II	Stages I and II	Stages I and II	Stage I	Stages I and II

UV: Ultraviolet

Table 6: Tissue and blood markers and their method of detection for various epithelial neoplasms

Tumor	Tissue markers	Blood markers	Method of analysis
Head-and-neck cancer	KERATINS EMA TPA Vimentin and desmin MMPS BMA P16 P53 MAC Interleukin-1ALPHA Endothelins CD 44	AFP, CEA, pancreatic oncofetal antigen 2. CA 125, CA 19-9, CA 15-3 Beta-human chorionic gonadotropin, calcitonin Albumin	Immunoassay Immunohistochemistry, PCR ELISA
Colorectal cancer	Microsatellite instability: MMR genes, MSH2, MLH1, MSH6 and PMS2 KRAS, EGFR, NRAS BRAF, PTEN, PIK3CA, ERCC-1 S100A2 protein	Microsatellite instability: MMR genes, MSH2, MLH1, MSH6 and PMS2 IGFBP2 Telomerase PKM2 Ezrin, P53, cyclooxygenase-2, 18q, LOH and TNIK	PCR ELISA PCR ELISA PCR IHC PCR, IHC, ELISA IHC
Breast cancer	ER, PR HER2 CA 15-3 Oncotype DX MammaPrint up A/PAI-1 Ki67	CA 15.3 CA 27.29 CA125 CEA Circulating tumor cells Human epididymis protein 4 Cyclin E Cathepsin D up A Leptin PAI-1 P53 CA 15-3	Immunoassay Immunohistochemistry
Liver cancer	GPC3 GPC3+heat shock protein Ki-67 MIB-1 E-cadherin β-catenin Plasma glutamate carboxy-peptidase, phospholipases A2 G13 and G7 and other cDNA microarray-derived encoded proteins Melanoma antigen gene 1, 3; synovial sarcoma on X chromosome 1, 2, 4, 5; sarcoplasmic calcium-binding protein 1;	AFP CEA Ferritin α1-antitrypsin α1-acid glycoprotein Osteopontin Aldolase A CK18, CK19, TPA, TPS Circulating free squamous cell carcinoma antigen-IgM complexes	Immunoassay Immunohistochemistry GENETIC MARKER PCR, ELISA
Bladder cancer	CKs 19 Survivin Telomerase BCLA 4 Microsatellite FGFR 3 Hyaluronic acid Hyaluronidase	HCE BETA CEA NMP22 BTA Stat 2 BTA Trak NMP22	Urine markers - immunoassay immunohistochemistry
Pancreatic cancer	Human equilibrative nucleoside transporter 1 MICRO RNA P16 P53 TELOMERASE S100 P	CA19-9 CEA MUC-4 MUC-1 CEACAM1 MIC1 CTC	Immunoassay Immunohistochemistry
Stomach cancer	CKs CYFRA 21.1, TPA, TPS β Subunit of HCG	CA19-9 CEA CA72-4	Immunoassay Immunohistochemistry

Contd...

Table 6: Contd...

Tumor	Tissue markers	Blood markers	Method of analysis
Esophageal cancer	HER2	BRAF	Immunohistochemistry, PCR
	PDL1	CA19-9	ELISA
		CEA	
Melanoma	MT DNA	S-100	Immunoassay
		BRAF	Immunohistochemistry
Cancer of female reproductive tract: cervical, uterine, ovarian	M-CSF	SCC	IMMUNOASSAY, ELISA
	HE4	CEA	Immunohistochemistry
	SAA	AFP	
		CA15-3	
		CA125	
Cancer of male reproductive organ: prostrate testis	PSA	PSA	Immunoassay
	PHI	AFP	Immunohistochemistry
	4KSCORE	HCG-BETA	
Lung cancer	NCAM, IL-2R, IGF-I, transferrin, ANP, mAb (cluster 5), CYFRA 21	CEA	Immunoassay, PCR, ELISA
		SCC	Immunohistochemistry, PCR, ELISA
		ALK	
		CYFRA 21-1	
Thyroid cancer	Galectin	Calcitonin	Immunoassay
	BRAF	CEA	Immunohistochemistry, PCR
		Thyroglobulin	

PCR: Polymerase Chain Reaction, IHC: Immunohistochemistry, ELISA: Enzyme-linked immunosorbent assay, CA: Cancer antigen, CEA: Carcinoembryonic antigen, ER: Estrogen receptor, PR: Progesterone receptor, p53: Tumor suppressor, HER: Heregulin, TPA: Serum tissue polypeptide antigen, TPS: Tissue polypeptide-specific antigen, BRAF: proto-oncogene B-Raf and v-Raf murine sarcoma viral oncogene homolog B, FOBT: The fecal occult blood test, EGFR: Epidermal growth factor receptor, KRAS: Kirsten rat sarcoma viral oncogene homolog, PIK3CA: Phosphatidylinositol 3-kinase, ALK: Anaplastic lymphoma kinase, PDL1: Programmed death-ligand 1, HE4: Human epididymis protein 4, OPN: Osteopontin, IGFR: Insulin-like growth factor receptor, VGEF: Vascular endothelial growth factor, MMP: Matrix metalloproteinase, MAGE: Tumor-specific antigen, ZEB: Zinc finger E-box binding homeobox, PTEN: Phosphatase and tensin homolog, BUB: Mitotic checkpoint protein, MYC: Basic helix-loop-helix protein, THCA: tetrahydrocannabinol acid, TSHR: Thyroid-stimulating hormone receptor, TTR: Transthyretin, GPC: Glypican, MIB: Cellular marker for proliferation, BTA: Bladder tumor antigen, HCG: Human chorionic gonadotropin, CYFRA: Cytokeratin fragment, PHI: Prostate Health Index, 4KSCORE: Kallikrein markers, ANP: Natriuretic peptide, SCC: Squamous cell carcinoma antigen, CK: Cytokeratin's, PSA: Prostate specific antigen, AFP: Alpha-fetoprotein, PKM2: Pyruvate kinase M2, IGFBP2: Insulin-Like Growth factor binding protein 2, LOH: Loss of Heterozygosity, TNIK: NICK-interactive kinase, PAI-1: Plasminogen activator inhibitor 1, up A: Urokinase plasminogen activator

Table 7: Proposed investigation protocol

Tumor	Blood markers
Head-and-neck cancer	SCC antigen
	CA 125
	CEA
	DNA ploidy
Lung cancer	FHIT
	ALK
Colorectal cancer	MLH 1, PTEN, MSH 2, MSH 6, MMR, KRAS
Male reproductive system	PSA
	PHI
Bladder cancer	HCG BETA, CEA, NMP22
Pancreatic cancer	CA19-9
Liver cancer	Alpha-fetoprotein, ERCC1
Thyroid cancer	Thyroglobin
Breast cancer	BRAC1, HE4, MIF, leptin, OPN, CA 125, p53
Female reproductive system	Microsatellite, P53, beta cantenin, PTEN, HER2/NEU, KRAS
Stomach cancer	CA 72-4
Esophageal cancer	CEA
	PDL1
Skin cancer	BRAF

CA: Cancer Antigen, CEA: Carcinoembryonic antigen, ER: Estrogen receptor, PR: Progesterone receptor, p53: tumor suppressor, HER: Heregulin, BRAF: Proto-oncogene B-Raf and v-Raf murine sarcoma viral oncogene homolog B, EGFR: Epidermal growth factor receptor, KRAS: Kirsten rat sarcoma viral oncogene homolog, PIK3CA: Phosphatidylinositol 3-kinase, ALK: Anaplastic lymphoma kinase, PDL1: Programmed death-ligand 1, HE4: Human epididymis protein 4, OPN: Osteopontin, PTEN: Phosphatase and tensin homolog, HCG: Human chorionic gonadotropin, CYFRA: Cytokeratin fragment, PHI: Prostate Health Index, SCC: Squamous cell carcinoma antigen, PSA: Prostate-specific antigen, AFP: Alpha-fetoprotein., FHIT: Fragile histidine triad

Conflicts of interest

There are no conflicts of interest.

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