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

INTRODUCTION

Epithelial neoplasm is an important global health-care problem, with high morbidity and mortality rates.[1,2] 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
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                                        |
| Cochrane   | 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                                     |
|            | Cancer of male reproductive tract AND tissue markers                                       |
|            | Thyroid cancer AND tissue markers                                                         |
|            | Pancreas cancer and tissue markers                                                        |
|            | 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: prostate testis | Lung cancer | Thyroid cancer | Gastrointestinal cancer | Skin cancer |
|-----------------------|----------------------|-------------------|---------------|--------------|---------------|------------------|-----------------------------------------------------------------|-----------------------------------------------|------------|----------------|----------------------------|------------|
| Author details        | Saleh K, Joshi P, Dutta, Shaw R, Perdomo S, Macfarlane T V, Omar EA | Buechler SA, Ye Z, Wang C, Mansfield CM Sharif J, Chen W, | Mohammadian M, Waller LP, Badievi S, Sia D, | Edmondson AJ, Pasin E, Barbosa LA, Metts MC, Soubra A, Shepard 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 | Tvera E, John R, Giudicessi | Factors R, Cooley ME, Holgate ST, Ganie F, Latimer KM, | Nguyen QT, Management C, Yusefi AR, Patients FOR, Bax MJ, Johnson TM, Rastrelli M, Das P, Melanoma C, Cancer S, Found B | Serious blistering sun burns UV radiation Family history Smoking, diabetes, alcohol consumption, obesity, decreased physical activity, decrease in the consumption of dairy products, decrease in the consumption of folate, fibers and Vitamin D |
| HPV                   | Fungal infection     |                           |               |              |               | 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                   |                       |                           |               |              |               | HP Virus: 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 |
| HPV                   |                       |                           |               |              |               | 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 |
|                        |                       |                           |               |              |               | HP Virus: Pylori HP Virus 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 |

Contd...
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: prostate testis | Lung cancer | Thyroid cancer | Gastrointestinal cancer | Skin cancer |
|---------------------------|----------------------|-------------------|---------------|-------------|---------------|------------------|-------------------------------------------------------------|--------------------------------------------------|------------|----------------|------------------------|-------------|
| Clinical signs and symptoms | Red/whitish patch ulcerative growth, Lump/mass without pain | Hoarseness | Frequent epistaxis | Difficulty in breathing | Difficulty in chewing/swallowing | Painful Nipple discharge | Blood discharge | Hematocrit Changes in the bladder habit | Urination changes in the lower extremity | Persistent cough | Decreased appetite | Nodule single/multiple | Irregularity of the mole |
|                          | Poly-p-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 | Nausea Vomiting Bloating Steatorrhea Abdominal pain Weight loss Jaundice Ascites Gastrointestinal bleeding | Back pain Edema in the lower extremity Uterine bleeding | Difficulty in urinating Prostate hypertrophy Back pain Hemoptyisis Gynecostasia | Fatigue Labored breathing Persistent cough Decreased appetite | Hoarseness of voice Wheeze, Stridor pneumonia | Nausea Vomiting Bleeding Ulcer Weight loss Steatorrhea Abdominal pain Bloating Dysphagia Dyspepsia | Irregularity of the mole |
|                          | Nipple discharge: blood discharge | Bladder fullness Weak urine stream Unable to urinate | Lower back ache Swelling in the feet | Hematuria Changes in the bladder habit Urinate more often Pain during urination | Back pain | Difficulty in urinating | Dysuria Bloating | | | | | |
|                          | | Hypercalcaemia | Hormonal imbalance GIT/esophageal bleeding | | | | | | | | | |
| Diagnosis                 | Stage I | Stage I | Stages II and III | Stage I | Stages II and III | Stage I | Stages I and II | Stages I and II | Stage I | Stages I and II | Stages I and II | Stage I |

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,  | TP 53                                                                     | P16                                                 |
|                        | Dahiya K, Negi M                                                                 | Rb                                                                        | 9pLOH                                               |
|                        | Soyano AE, Kanik P                                                              | I7 LOH                                                                    |                                                     |
|                        |                                                                                 | APC -5q21-22                                                              |                                                     |
|                        |                                                                                 | Mismatch MSH 2, MSH3, MLH1                                                |                                                     |
|                        |                                                                                 | PMS 1                                                                     |                                                     |
|                        |                                                                                 | MSH 6                                                                     |                                                     |
| Colorectal cancer      | Soyano AE, Kanik P                                                              | LOH at multi loci                                                         |                                                     |
|                        |                                                                                 | BRCA1                                                                     |                                                     |
|                        |                                                                                 | BRCA 2                                                                    |                                                     |
|                        |                                                                                 | Estrogen receptor - positive                                             |                                                     |
|                        |                                                                                 | P53 mutation                                                              |                                                     |
|                        |                                                                                 | Heterozygosity ATM                                                       |                                                     |
|                        |                                                                                 | P53                                                                       |                                                     |
|                        |                                                                                 | cerbB2                                                                    |                                                     |
|                        |                                                                                 | BCL                                                                        |                                                     |
| Breast cancer          | Hou L, Myp C, Sporikova Z                                                        | LOH at multi loci                                                        | Ki67                                                |
|                        |                                                                                 | BRCA1                                                                     | MIB 1                                               |
|                        |                                                                                 | BRCA 2                                                                    | Topoisomerase                                        |
|                        |                                                                                 | Estrogen receptor - positive                                             | histone H3                                           |
|                        |                                                                                 | P53                                                                       |                                                     |
|                        |                                                                                 | P16                                                                        |                                                     |
|                        |                                                                                 | P15                                                                        |                                                     |
|                        |                                                                                 | BUB 1                                                                     |                                                     |
|                        |                                                                                 | Cyclin D                                                                  |                                                     |
|                        |                                                                                 | Mismatch MSH 2, MSH3, MLH1                                                |                                                     |
|                        |                                                                                 | PMS 1                                                                     |                                                     |
|                        |                                                                                 | MSH 6                                                                     |                                                     |
|                        |                                                                                 | 9pLOH                                                                     |                                                     |
| Liver cancer           | Daher S                                                                         | Adenomatous hyperplasia                                                  |                                                     |
|                        |                                                                                 | Alpha-fetoprotein                                                        |                                                     |
| 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                                                                        |                                                     |
| Pancreatic cancer      | Duffy MJ, Gooneseckere NCW, Zapata M, Smith RA, Loosen SH, Hamada S, Malati T | Mutation of trypsinogen gene - 7q35                                       |                                                     |
|                        |                                                                                 | BRCA2                                                                     |                                                     |
|                        |                                                                                 | P16                                                                        |                                                     |
| 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                                                          |                                                     |
### 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 receptor1, Cdkn2a mutation, P16, CDK 4, CDKN2, PTEN, 1p, 6q, 7p, 11q, P53, Myc, BRAF | CDK 1, MC 1P, P53, MYC                |
| Cancer of female reproductive tract: cervical, uterine, ovarian | Dong X, Prat J, Wang T, Rein BJ D | CIN 1,2,3,4, Diploid/polyoid associated with HPV, c-myc, N-MYC, KRAS, FHit, CYT P141, C-ERBB2, PTEN, LOH 3P | HPV, FHit, P53, KRAS, MYC, P16, PTEN, BRCA |
| Lung cancer                                | Inamura K, Cheng L, Travis WD   | Polymorphism of cytochrome p450 gene, P 53 mutation, Isocero 12p, Cyclin D, P53, P53 | TP 53, BCL2, KRAS, CDKN2a, P16, LOH 3P |
| 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, 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, P145: Multiple tumor suppressor gene, CD 44: Cell surface glycoprotein, cell-cell interactions, BRCA: Breast cancer gene, ATM: Ataxia-telangiectasia mutated, cerB2: 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, MMK: 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-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.\[^{11-149}\]
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 PS3 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            | Tissue (IHC)     | Breast cancer and its subtypes                 |
| Seyedabbsmirmalek et al.       | HER 2 PS3        | Tissue (IHC)     | Breast cancer and its subtypes                 |
| Michael j. Duffy               | CA 15-3 BR 27.29 | 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  | Blood            | Colorectal cancers                             |
| Gadeppali et al.               | EGFR             | Blood            | Colorectal cancers                             |
| Chan dihedral                  | EGFR ALK AND its | Blood            | Colorectal cancer                              |
| Jincheng et al.                | EGFR             | Blood            | Lung                                           |
| Gilda da concha santos         | EGFR             | Blood and tissues | Lung                                           |
| Fernando c. Santini et al.     | PD1              | Blood and tissues | Lung                                           |
| D.Ed. Meyers et al.            | PD-1/PD-L1 AXSIS| Blood and tissues | Lung                                           |
| Oliver Dorigo et al.           | CA 125           | 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.               | IGF              | Serum            | Pancreas                                       |
| G.talar-wojnarowska et al.     | VEGF             | Serum            | Pancreas                                       |
| Leonard s. Marks et al.        | PCA3             | Blood            | Prostate                                       |
| Dragan Iliac et al.            | PSA              | Blood            | Prostate                                       |
| Ji-fan lin et al.              | MICRO RNA        | Blood            | Bladder cancer                                 |
| Weige tan et al.               | MICRO RNA25      | 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/ saliva | Head and cancer                               |
| Kiran Dahiya et al.            | Chemokine receptor MMP HPV Interleukin MicroRNA MAGE Actin and myosin | Tissue/ saliva | Head and cancer                               |
| Esam Ahmad Omar                | KRAS PTEN P21 miRNA | Blood | Head and cancer                               |

Contd...
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 | Colon cancer | Breast cancer | Liver cancer | Bladder cancer | Pancreatic cancer | Cancer of female reproductive tract: cervical, uterine, ovarian | Lung cancer | Thyroid cancer | Gastrointestinal cancer | Skin cancer |
|---------------------------|----------------------|--------------|--------------|--------------|----------------|------------------|---------------------------------------------------------------|------------|----------------|--------------------------|-------------|
| Specific etiological factors | HPV, Fungal infection | HPV, Fungal infection | HPV, Fungal infection | HPV, Fungal infection | HPV, Fungal infection | HPV, Fungal infection | HPV, Fungal infection | Selenium | Androgens | Asbestos | HPV, Fungal infection |
| Specific clinical signs and symptoms | Red/whitish patch, Ulcerative growth, Lump/mass without pain | Hematuria, Changes in the bladder habit | Nausea, Vomiting | Back pain | Difficulty in urinating | Labored breathing, Persistent cough | Nodule (single/multiple) | Nausea, Vomiting | Bleeding | Dysphagia | Dyspepsia |

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       | AFP, CEA, pancreatic oncofetal antigen 2.                                   | Immunoassay                             |
|                            | EMA            | CA125, CA19-9, CA15-3                                                       | Immunohistochemistry, PCR               |
|                            | TPA            | Betahuman chorionic gonadotropin, calcitonin                                | ELISA                                   |
|                            | Vimentin and desmin |                                                                                   |                                         |
|                            | MMP5           |                                                                                   |                                         |
|                            | BMA            |                                                                                   |                                         |
|                            | P16            |                                                                                   |                                         |
|                            | P53            |                                                                                   |                                         |
|                            | MAC            |                                                                                   |                                         |
|                            | Interleukin-1ALPHA |                                                                                   |                                         |
|                            | CD 44          |                                                                                   |                                         |
|                            | Endothelins    |                                                                                   |                                         |
|                            |                |                                                                                   |                                         |
| Colorectal cancer          | Microsatellite instability: MMR genes, MSH2, MLH1, MSH6 and PMS2 | MicrOSatellite instability: MMR genes, MSH2, MLH1, MSH6 and PMS2 | PCR                                     |
|                            | KRAS, EGFR, NRAS |                                                                                   | ELISA                                   |
|                            | BRAF, PTEN, PIK3CA, ERCC-1 |                                                                                   | PCR                                     |
|                            | S100A2 protein |                                                                                   | PCR                                     |
|                            |                |                                                                                   | IHC                                     |
|                            |                |                                                                                   | PCR, IHC, ELISA                         |
|                            |                |                                                                                   | IHC                                     |
| Breast cancer              | ER, PR         | CA 15.3                                                                         | Immunoassay                             |
|                            | HER2           | CA 27.29                                                                        | Immunohistochemistry                    |
|                            | CA 15-3        | CA125                                                                           |                                          |
|                            | Oncotype DX    | CEA                                                                              |                                          |
|                            | MammaPrint     | Circulating tumor cells                                                         |                                          |
|                            | up A/PAI-1     | Human epidermis protein 4                                                        |                                          |
|                            | Ki67           | Cyclin E                                                                        |                                          |
|                            |                | Cathepsin D                                                                      |                                          |
|                            |                | Leptin                                                                           |                                          |
|                            |                | PAI-1                                                                            |                                          |
|                            |                | P53                                                                              |                                          |
|                            |                | CA 15-3                                                                          |                                          |
| Liver cancer               | GPC3           | AFP                                                                             | Immunoassay                             |
|                            | GPC3+heat shock protein |                                                                                   | Immunohistochemistry                    |
|                            | Ki-67          | CEA                                                                              | PCR, ELISA                              |
|                            | MiB-1          | Ferritin                                                                         |                                          |
|                            | E-cadherin     | a1-antitrypsin                                                                  |                                          |
|                            | b-catenin      | a1-acid glycoprotein                                                             |                                          |
|                            | Plasma glutamate carboxy-peptidase, phospholipases A2 G13 and G7 and other cDNA microarray-derived encoded proteins | Osteopontin                           |                                          |
|                            | Melanoma antigen gene 1, 3; synovial sarcoma on X chromosome 1, 2, 4, 5; sarcoplasmic calcium-binding protein 1; | Aldolase A                             |                                          |
|                            |                |                                                                                   |                                          |
| Bladder cancer             | CKs 19         |                                                                                   |                                          |
|                            | Survivin       |                                                                                   |                                          |
|                            | Telomerase     |                                                                                   |                                          |
|                            | BCLA 4         |                                                                                   |                                          |
|                            | Microsatellite |                                                                                   |                                          |
|                            | FGFR 3         |                                                                                   |                                          |
|                            | Hyaluronic acid |                                                                                   |                                          |
|                            | Hyaluronidase  |                                                                                   |                                          |
|                            |                |                                                                                   |                                          |
| Pancreatic cancer          | Human equilibrative nucleoside transporter 1 |                                                                                   |                                          |
|                            | MICRO RNA      |                                                                                   |                                          |
|                            | P16            |                                                                                   |                                          |
|                            | P53            |                                                                                   |                                          |
|                            | TELOMERASE     |                                                                                   |                                          |
|                            | S100 P         |                                                                                   |                                          |
|                            |                |                                                                                   |                                          |
| Stomach cancer             | CKs            |                                                                                   |                                          |
|                            | CYFRA 2.1, TPA, TPS |                                                                                   |                                          |
|                            | β Subunit of HCG |                                                                                   |                                          |
|                            |                |                                                                                   |                                          |

Contd...
Table 6: Contd...

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

Table 7: Proposed investigation protocol

| Tumor                  | Blood markers               |
|------------------------|----------------------------|
| Head-and-neck cancer   | SCC antigen, CA 125, CEA    |
|                        | DNA ploidy, FHIT, ALK       |
| Lung cancer            | MLI 1, PTEN, MSH 2, MSH 6, MMR, KRAS |
|                        | PSA, PHI, HCG, CEA, CEA, NMP22 |
| Colorectal cancer      | MLH 1, PTEN, MSH 2, MSH 6, MMR, KRAS |
| Male reproductive system | PSA, PHI                   |
| Bladder cancer         | HCG, CEA, NMP22            |
| Pancreatic cancer       | CA 19-9                    |
| Liver cancer           | Alpha-fetoprotein, ERCC1    |
| Thyroid cancer         | Thyroglobin                 |
| Breast cancer          | BRAC1, HE4, MIF, leptin, OPN, CA 125, p53 |
| Female reproductive system | Microsatellite, P53, beta cstenin, PTEN, HER2/NEU, KRAS |
| Stomach cancer         | CA 72-4                    |
| Esophageal cancer      | CEA                        |
|                        | PDL 1                      |
|                        | BRAF                       |

Conflicts of interest

There are no conflicts of interest.

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