

Chapter 2

Head and Neck Cancer Prevention

Fausto Chiesa, Angelo Ostuni, Roberto Grigolato, and Luca Calabrese

Abstract Head and neck cancer (HNC) represents a broad spectrum of diseases that involves the nasal and oropharyngeal cavities, the paranasal sinuses, the major and minor salivary glands, the larynx and the lymphatic tissues of the neck. The world-wide yearly incidence exceeds over half a million cases. Tobacco (smoking and smokeless) and alcohol use are the principal risk factors, however, a substantial and increasing proportion of head and neck tumors cannot be attributed to these. Recent evidence has shown that the incidence of oropharyngeal cancer among women and younger patients continues to grow and it is not related to alcohol or tobacco use but to human papillomavirus infection. Substantial advances in treatment regimens made over the last two decades have not improved the 5-year mortality rate that remains approximately 50%.

Prevention represents the best opportunity to improve oncologic results and it consists of three levels of intervention: primary prevention (considered the best) aims to avoid exposure to established risk factors; secondary prevention consists of early diagnosis; tertiary prevention involves active management of patients already treated for HNC.

In this chapter, we review the natural history of oral cavity and laryngeal cancer as well as the known mechanisms of carcinogenesis. Precancer and risk markers for cancer are discussed as they relate to prevention in all its forms (primary, secondary, and tertiary). Chemoprevention is the use of natural or synthetic chemicals to reverse, suppress, or prevent the conversion of a premalignant lesion to a true neoplasm. It spans all three forms of prevention and it can aim at both local and locoregional disease control. All of the major important chemoprevention clinical trials reported on in the scientific literature are presented and discussed critically and their impact on clinical practice is presented.

Attention is given to new directions in the field and how HNC prevention may progress through the search for new, sensitive, and specific biomarkers as well as an improved understanding of the biomolecular mechanisms of tumor invasion, metastasis, and the newly acquired data from the Human Genome Project.

Improvement in HNC prevention requires a multidisciplinary approach to face complex processes and multiple factors that may act concurrently in the etiology of disease. Future challenges remain in the correct interpretation of new findings and their wise and scientific application. Only then will we be able to impact the field of HNC, transforming prevention in the only form of cure.

Keywords Prevention • Early diagnosis • Chemoprevention • Precancerous lesions • Risk factors • HPV • Biomarkers • Molecular medicine • Multidisciplinary approach

Introduction

Head and neck cancer (HNC) represents a broad spectrum of diseases that involves the nasal and oropharyngeal cavities, the paranasal sinuses, the major and minor salivary glands, the larynx and the lymphatic tissues of the neck. The world-wide yearly incidence exceeds over half a million cases [1]. Tobacco (smoking and smokeless) and alcohol use are the principal risk factors, however, a substantial and increasing proportion of head and neck tumors cannot be attributed to these. Recent evidence has shown that the incidence of oropharyngeal cancer among women and younger patients continues to grow and it is not related to alcohol or tobacco use but to human papillomavirus (HPV) infection [1–5].

Substantial advances in treatment regimens made over the last two decades have not changed the 5-year mortality rate that remains approximately 50% [6–11]. The diagnosis of HNC is often dramatically delayed in spite of easy access for evaluation and screening [12–14]. Late diagnosis results in complex, aggressive, and often mutilating treatment with a

F. Chiesa (✉)
Department of Head and Neck Surgery, European Institute of
Oncology, Via Ripamonti, 435, Milano 20141, Italy
e-mail: fausto.chiesa@ieo.it

high morbidity and significant functional compromise. Local disease control (e.g., minimizing metastases and managing recurrence) and development of a second primary tumor remain two of the most significant challenges [15, 16]. In fact, second primary tumors are among the major cause of morbidity and mortality among patients cured for head and neck squamous cell carcinomas (HNSCC).

Prevention of HNC could offer the best opportunity to improve oncologic results and it consists of three levels of intervention. Primary prevention aims at avoiding exposure to established risk factors. Approximately 80% of HNCs are tobacco and alcohol related [1–3]; this percentage is not so easy to reduce because of the addiction induced by their daily use and the powerful impact of advertising by the tobacco and liquor industry particularly on the younger population. The increased incidence of HPV-related cancers has been linked to a change in the sexual patterns in the overall population. Currently, other than monogamous sexual intercourse and avoidance of orogenital intercourse, no effective strategies exist to eliminate this risk factor.

Secondary prevention consists of early diagnosis. Early detection programs usually entail regular clinical evaluation of asymptomatic at-risk patients; consistent and reliable instrumental or serologic tools are currently unavailable. Even though screening is not equally successful for all HNCs, the premise is that early diagnosis could improve morbidity and mortality outcomes. Improved screening increases the overall number of diagnoses, however, in order to be truly effective, it must be associated with increased disease-free survival, a decreased mortality rate, and improvement in the effectiveness of treatments. If this is not possible, and the patient's quality of life does not improve, the cost–benefit ratio may be too high to be justified [17].

Tertiary prevention involves management of patients already treated for HNC. The interventions range from educational programs to smoking cessation for those patients who continue to smoke even with the diagnosis of a malignancy and include early diagnosis of recurrences and/or second primary tumors.

Natural History of Head and Neck Cancers

Head and Neck Carcinogenesis

The development of HNCs is generally related to field cancerization and multistep carcinogenesis. Field cancerization is a morphological concept arising from Slaughter's observation that in all resected oral tumors, the macroscopically

benign epithelium beyond the periphery of the primary tumor was microscopically abnormal [18]. Exposure of an epithelial field to repeated carcinogenic insults results in the development of genetic damage to normal-appearing mucosa. The entire field is susceptible to multifocal development of squamous intraepithelial neoplasia (SIN) and cancer [18–21]. A distinct but related concept is “the field of tissue injury,” which includes the molecular changes occurring throughout the tissue exposed to a carcinogen [22]. The field of injury reflects the host's response to and damage from the carcinogen; this may or may not be a precursor to premalignant lesions and frank malignancy. Field cancerization and the field of injury have both been implicated in many malignancies and potentially hold the keys for preventing and curing epithelial cancers and for understanding *in vivo* epithelial carcinogenesis. Target treatments to reduce cancer risk involve the whole field.

On a molecular level cancer is considered a disease of genetic, progressive, multistep mutation [23–29], however, carcinogenesis may take multiple paths and may be multifocal. This progression is heralded in tissues by the appearance of associated specific molecular and genotypic damage resulting in phenotypic changes that progress from normal histology to early dysplasia, continuing on to severe dysplasia, superficial cancers, and finally invasive disease [23, 24]. It has been estimated that four to six genetic events are required to progress from severe dysplasia to cancer and that one HNC could require up to 10–20 years to develop. The degenerative advance of cancer, however, is not always linear or sequentially additive: progression can occur away from clinically visible lesions, strongly suggesting that genetic aberrations may not always result in locally apparent disease and accumulation of mutations. Lesions that appear morphologically similar harbor often different molecular fingerprints, suggesting that a given phenotypic change can arise from diverse pathways. This absence of a direct, predictable, and consistent correlation between clinical and histological features of suspect lesions is well documented [23–29]. Recent microarray investigations of chromosomal aberration patterns of HPV-negative oral and oropharyngeal squamous cell carcinomas showed subclasses of cancer with unique genetic and clinical fingerprints. This observation, if confirmed in larger studies, could have important diagnostic and therapeutic implication in clinical practice [30].

Precancerous Lesions

Epidemiological, experimental, and clinical observations teach us that cancer may be preceded by a morphological tissue modification, a precancerous lesion, clinically manifest

as a white (leukoplakia), a red (erythroplakia), or a red-white lesion (erythro-leukoplakia).

Oral Cavity

Leukoplakias and Related Lesions

White lesions in the oral cavity were thought to be precancerous as early as 1870 by Paget, who described them as ichthyosis, smoker's patch, and leucokeratosis [31]. The term leukoplakia was first used by Schwimmer in 1877 [32]. In 1936, McCarthy described the microscopic features of oral leukoplakias, grading them as 1–4, where grade 4 referred to lesions showing microscopic evidence of significant dysplasia or early malignant changes [33].

Leukoplakia is a clinical term used to describe a range of white oral lesions; it implies a diagnosis of exclusion of common conditions with similar appearance and harbors intrinsic potential malignancy [34–37]. Microscopically, these lesions are characterized by simple orthokeratosis, parakeratosis with epithelial hyperplasia and minimal inflammation, hyperkeratosis, or varying degrees of dysplasia. The latter occurs in up to 16% of leukoplakias [34]. Leukoplakias and erythroplakias (less frequent than leukoplakias in the general population) may undergo malignant transformations with or without clinical evidence of such change. Only 5–36% of white lesions can transform into malignancy within 20 years, the annual transformation rate of oral leukoplakia is unlikely to exceed 1%, and there is no proven correlation between transformation and the degree of dysplasia [38–41]. In spite of the progresses in molecular biology, there is not yet a single reliable marker predictive of malignant transformation [36, 37]. Clinically, early stages may be mistaken for reactive lesions that appear either as painless, nonhealing, indurated ulcerations, or hypertrophic lesions. Differential diagnosis is based on the analysis of the risk factors, the natural history, the progression and, most importantly, the clinical features of the lesion. A definitive diagnosis, however, can only be obtained after histological confirmation. Only then can the appropriate therapy be selected. The clinical conundrum for lesions without features of malignancy remains whether the initial biopsy is representative of the entire lesion, especially when they present with nonhomogeneous features [38, 42]. Microscopic foci of malignant tissue may be present and can only be detected histologically. Unexpected carcinomas in resection specimen have been reported for oral lesions removed after the initial incisional biopsy had not shown the presence of malignant tissue [38–43]. This lack of correlation between the histopathologic examination of

initial biopsies and the examination of definitive surgical specimens may strongly influence the decision-making process when assessing and managing suspicious lesions [42, 44].

Conventional Treatment of Leukoplakias and Related Lesions

In consideration of the reported malignant transformation rate of 5–36% [38–41], the therapeutic goal for oral leukoplakias is secondary prevention. Treatment modalities include lifestyle modification and elimination of risk factors, such as tobacco and alcohol intake, medical therapy with retinoids or antimycotics, surgical excision, cryosurgery, laser evaporation, or laser excision. Surgical excision is widely accepted to be the most effective form of treatment [36–44]. A useful initial approach in the management of oral leukoplakias should be the removal of etiologic factors in conjunction with simultaneous anti-inflammatory and antimycotic therapy. If clinical improvement or resolution is not obtained within a few weeks, surgical excision of persistent oral leukoplakias, preferably laser resection, seems to be the most rational next step [45]. However, results of prospective [46] and retrospective studies [36–45] describing rates of malignant transformation in patients treated with surgical or laser excision of oral leukoplakias are hardly comparable because of differences in diagnostic and inclusion criteria, follow-up time intervals, patient characteristics, and surgical techniques employed. The inconclusive data leaves unproven the hypothesis that surgical removal of potentially malignant oral lesions can prevent the onset of oral cancer [37, 38, 41, 47–49] and formed the basis for pilot chemoprevention studies.

Larynx

Leukoplakias and Related Lesions

Analogies exist between laryngeal and oral precancerous lesions: the presence of dysplasia has clinical relevance for both, but in laryngeal lesions a better correlation seems to exist between the grade of dysplasia and the clinical evolution of the lesion [50–54]. The natural history of untreated laryngeal dysplasia is well described for mild and moderate dysplasia. Invasive cancer can develop in as many as 45% of patients with moderate dysplasia and some authors have recommended intervention. For lesions with mild dysplasia, the rate of progression is reported to be up to 11.5% [49, 53].

Conventional Treatment of Leukoplakias and Related Lesions

As for the oral cavity, the management of premalignant lesions of the larynx is controversial. The best opportunity for cure must not be missed because of inadequate treatment and therapy must be oncologically radical with maximal functional preservation. The available data on the treatment of laryngeal premalignancy mostly addresses severe dysplasia/carcinoma in situ [51–56]. A “wait-and-see” approach cannot be employed in these patients as some studies have indicated an unacceptably high rate of progression to invasive carcinoma. Intervention is recommended for all cases of severe dysplasia and/or carcinoma in situ [54]. Despite substantial recent advances there is significant morbidity associated with nonsurgical therapy sometimes used to treat these conditions [56] while laser surgery seems to be the best treatment modality to fulfill the requirements of oncologic radicality and organ as well as functional preservation [51, 52, 55].

Precancer and Risk Markers for Cancer

A biological marker (biomarker) is a parameter that can be objectively measured and evaluated as an indicator of normal biological and pathogenic processes, gauging the response to therapeutic (most often pharmacological) interventions [57]. A small subset of biomarkers that demonstrate a strong correlation with the desired clinical endpoint can serve as its substitute. These surrogate endpoints are expected to be reasonably likely to predict clinical benefit or harm (or lack thereof) based on epidemiologic, therapeutic, physiopathologic, or other scientific evidence.

The search for reliable biomarkers has an important impact on the evaluation of chemoprevention studies that goes beyond the potential changes to clinical practice. The evaluation of a marker linked to carcinogenesis requires the study of its expression in tumors; the presence of this marker (over-expressed, mutated, or masked) is analyzed in precancerous lesions or in normal tissue to assess if it is present as an indicator of a biologic process associated with the progression of a neoplasia [58]. In HNC chemoprevention trials, the search for reliable biomarkers focuses on identification of indicators of malignant transformation in clinically suspect lesions, those linked to second primary tumors and/or identification of individuals at greatest risk for the development of neoplasias [58]. SIN is defined as a noninvasive lesion with genetic abnormalities resulting in loss of cellular control functions with some phenotypic characteristics of invasive cancer [35, 59]. Preventive measures focus on evaluation and removal of its risk factors and surgical resection [45, 49, 51]. Epithelial tissues display SIN as moderate to severe dysplasia whose grade is determined by the degree of cellular abnormality above

the epithelial basement membrane [34–38, 59]. Accuracy in grading is dependent on the quality of the tissue sample, the biopsy site, and the experience of the pathologist. Several studies have shown great inter- and intra-examiner variability in the assessment of presence, absence, and grade of oral epithelial dysplasia [35, 37, 59]. SIN is believed to represent (with appropriate sampling) the total field of abnormal epithelium and to provide identifiable lesions that can be targeted to evaluate the efficacy of new therapeutic interventions [28]. However, only a small portion of these lesions progress to cancer and they are not always indicative of malignant transformations [38, 42]. A striking discordance between the genetic status and the clinical and histologic features has been reported, particularly as it relates to treatment response [60]. Molecular studies also suggest that dysplasia may not be considered a reliable biomarker for cancer because high risk modifications can be found in nondysplastic lesions [49, 58].

There currently is not a body of evidence substantially strong enough to advocate in clinical practice the use of biomarkers as prognostic indicators for HNC [58]. Research in the field continues particularly with gene expression and salivary proteomics studies [61, 62] and recently published reports identify Podoplanin [63, 64] and the genotype CD1 AA and AG [54] as promising new markers.

Chemoprevention

Chemoprevention is the use of natural or synthetic chemicals for the reversal, suppression, or prevention of conversion of a premalignant lesion to an invasive form [57]. In other words, chemoprevention includes all the interventions that employ agents aimed at preventing the development of cancer. Two basic concepts guide chemoprevention studies; the levels of acceptable toxicity must be much lower than in patients with cancers and the drug may only be administered orally [57, 65]. Premalignant lesions of the oral cavity represent an ideal model to study chemoprevention. Ready access allows easy monitoring and serial biopsies resulting in greater possibility of early intervention and faster data analysis [66, 67]. Only few studies have been conducted on laryngeal precancer because of limitations related to difficulty in access and monitoring [54, 68–70]. We can distinguish different forms of chemopreventive interventions: primary, adjuvant, and chemoprevention in high-risk population.

Primary Chemoprevention

This form of chemoprevention includes treatment of precancerous lesions (leukoplakias) with agents acting to reverse morphological precursors of malignancy and to assess their efficacy.

Table 2.1 Primary chemoprevention randomized trials

<i>Stich HF, 1988 [75]</i>	
Design	β -Carotene 180 mg/week (Group I), β -carotene+ vitamin A 100,000 IU/week (Group II), placebo (Group III)
Length of the study	6 months
Patients included in the study	130 tobacco/betel chewers
End points	Complete remission (RC) of lkp and reduction of micronucleated cells
Results	Group I = 15%, Group II = 27% ^a , Group III = 3%
Remarks	Nobody changed the risk habits
<i>Stich HF, 1988 [76]</i>	
Design	Vitamin A 200,000 IU/week vs. placebo
Length of the study	6 months
Patients included in the study	54 tobacco/betel chewers
End points	Complete remission (RC) of lkp and prevention of new lkp
Results	Intervention group = 57% RC, 0% New lkp; Placebo = 3% RC, 21% New lkp
Remarks	Nobody changed the risk habits
<i>Hong WK, 1986 [66]</i>	
Design	13- <i>cis</i> -RA (1–2 mg/kg/day) vs. placebo
Length of the study	3-month intervention; follow-up = 6 months
Patients included in the study	Intervention = 24; placebo = 20
End points	Clinical = remission of leukoplakia; pathological = reversion of dysplasia
Results	Clinical-intervention group = 67%, placebo = 10%, $p = 0.0002$; pathological-intervention group = 54%, placebo = 10%; $p = 0.01$
Remarks	Two severe toxicity; relapse of lkps in 56% of responding patients 2–3 months after intervention ended
<i>Lippman SM, 1993 [77]</i>	
Design	Phase I = 3-month high-dose 13- <i>cis</i> -RA (1.5 mg/kg/day) Phase II = 9-month low dose 13- <i>cis</i> -RA (0.5 mg/kg/day) (Group I); β -carotene (30 mg/day) (Group II)
Length of the study	12 months
Patients included in the study	Phase I (3 months) = 70; phase II (9 months) = 33 Group I, 26 Group II
End points	Remission of leukoplakia
Results	Phase I – remission of lkp = 36/66 (55%); progression of lkp = 7/66 Phase II – remission or stable disease 92% Group I vs. 45% Group II; $p = 0.001$ Group I = 8% progression, 1 Tis; Group II = 55% progression, 1 Tis, 5 SCC
Remarks	Mild, though greater toxicity in the high-dose 13- <i>cis</i> -RA evaluable patients after phase I (3 months) = 66; after phase II = 22 (Group I); 13 (Group II)

lkp leukoplakia, *is* in situ carcinoma, SCC squamous cell carcinoma

^a Statistically significant

Retinoids, β -carotene, and α -tocopherol are the main agents employed in chemoprevention studies of oral leukoplakias. More than 30 years have elapsed since the initial clinical studies of natural vitamin A in the management of oral leukoplakia, and several single-arm studies have been reported [71–74]. Table 2.1 shows the design and the results of the published randomized trials [66, 75–77]. These studies demonstrate response rates that vary from 44 to 83% but revealed the dermatologic and liver toxicity of natural vitamin A. The effectiveness of these interventions is limited to the duration of the drug intake: a few weeks or months after stopping the drug intake the leukoplakias recur. Topical application of a natural or synthetic retinoid also achieved a temporary complete remission in more than 50% of patients, but the severe local side effects and the necessity to apply the drug locally limited this form of treatment and it is no longer used [45, 74]. Several authors conducted chemoprevention trials for laryngeal precancerous lesions [68, 69, 78]. The efficacy of the chemopreventive agents was less (clinical and histologic) than in oral lesions while similarities were noted in the overall

response profile (variability of response rate, side effects). Among these studies particular attention should be given to the Almadori trial [78]: a chemoprevention study with folates in patients with oral and laryngeal leukoplakias based on the observation that serum folate levels are significantly lower in patients with cancerous and precancerous lesions than in at risk and control patients.

While there currently is no effective form of primary chemoprevention, its main role and goal remains to evaluate and test new agents that are effective and have a low side-effect profile.

Adjuvant Chemoprevention: Prevention of Second Primary Tumors

This form of chemoprevention consists of interventions on patients cured for HNC that employ a chemopreventive agent or a combination of agents in order to reduce the risk of second

primaries. Patients treated for HNC have a constant and continuing risk of developing a second primary that varies from 2.7 to 4% yearly in the aerodigestive tract as well as in other sites [15, 16, 20, 79, 80]. Adjuvant chemoprevention might modulate epithelial cell biology and this way halt the progression of carcinogenesis [17, 81].

The development of synthetic vitamin A analogs (all-*trans*-retinoic acid, 13-*cis*-retinoic acid, etretinate, and phenretinide)

with potentially greater therapeutic indexes allowed the rapid expansion of chemoprevention trials [66, 77, 82]. Design and results of the published randomized trials are reported in Table 2.2 [67, 82–89]: in most of these the treatment regimens synthetic retinoids are taken alone or in association with β -carotene. The reported protective effects are conflicting: in some studies retinoids seem to significantly reduce occurrence of second primaries [67, 82, 83], in others

Table 2.2 Adjuvant chemoprevention: results of the most significant randomized trials

Hong WK, 1990 [82], Benner SE, 1994 [83]

Design	13- <i>cis</i> -RA (50–100 mg/m ² /day) for 12 months vs. placebo
Length of the study	Intervention = 12 months; follow-up = 54.5 months (median)
Patients included in the study	103 disease-free patients after primary treatment for a HNSCC
End point	Occurrence of second primaries
Results	Intervention = 4%; placebo = 24%; $p = 0.005$
Remarks	13- <i>cis</i> -RA does not prevent recurrences and progression of the original tumor Difference in developing a second primary between treatment group diminishes in time, however, persists reduction of occurrence of second primary within head and neck area and lung

Bolla M, 1994 [84]

Design	Etretinate (50 mg/day first month, and 25 mg/day 23 months) vs. placebo
Length of the study	Intervention = 12 months; follow-up = 41 months (Median, range 0–81)
Patients included in the study	316 patients treated for T1/T2 N0/N1 ≤ 3 cm M0 HNSCC
End point	Occurrence of second primaries
Results	No differences between intervention group (28 second primaries) and placebo (29 second primaries)
Remarks	Multicentric study Treatment discontinued in 33% of patients due to toxicity vs. 23% in placebo, $p = 0.05$ Etretinate does not prevent recurrences and progression of the original tumor

van Zandwijk N, 2000 [85]

Design	Group I – <i>N</i> -acetyl cysteine (600 mg/day/2 years); Group II – retinol palmitate (300,000 IU/day/1 year and 150,000 IU/day/1 year); Group III – both; Group IV – placebo
Length of the study	Intervention = 24 months; follow-up = 49 months (Median)
Patients included in the study	2,595 patients treated for curable HNSCC (60%) and lung cancer (40%)
End points	Occurrence of second primaries and recurrences of the treated tumor
Results	No differences between the four groups
Remarks	Multicentric study 93.5% of patients have smoked; 25% continued to smoke after cancer diagnosis

Bairati I, 2005 [86], Meyer F, 2008 [87]

Design	α -Tocopherol (400 IU/day) and β -carotene (30 mg/day) + RT vs. Placebo + RT
Length of the study	Intervention = 36 months; follow-up = 52 months (Median)
Patients included in the study	400 with stage I–II HNSCC treated by radiation therapy
End points	Occurrence of second primaries and recurrences of the treated tumor
Results	α -Tocopherol higher risk than placebo of second primary (HR = 2.88) and recurrences (HR = 1.86) during the supplementation period, but lower rate when supplementation was discontinued (second primary HR = 0.41; recurrences HR = 0.33). Among smokers during RT highest risk of death for HNSCC (HR = 3.38)
Remarks	Multicentric study In the course of the trial β -carotene was discontinued after 156 patients had enrolled because of ethical concerns

Khuri FR, 2006 [88]

Design	13- <i>cis</i> -RA (30 mg/m ² /day) vs. Placebo
Length of the study	Intervention = 36 months, monitored for up to 4 years
Patients included in the study	1,190 early stage (I–II) HNSCC
End point	Occurrence of second primaries and overall survival
Results	No statistical difference
Remarks	Smoking statistically significantly increased the rate of second primary (HR = 1.64) and death (HR = 2.51) than nonsmoking (HR = 2.52)

(continued)

Table 2.2 (continued)*Perry CF, 2005 [89]*

Design	Group I=high-dose isotretinoin (1 mg/kg/day for 1 year and 0.5 mg/kg/day for 2 years); Group II=moderate dose isotretinoin (0.5 mg/kg/day); placebo
Length of the study	3 years intervention
Patients included in the study	151 patients cured for a HNSCC
End points	Occurrence of second primary in head and neck are lung or bladder
Results	No significant difference in the occurrence of second primary, recurrence of primary disease or DFS
Remarks	Multicentric trial

Chiesa F, 2005 [67]

Design	Fenretinide 200 mg (1 year) vs. Placebo
Length of the study	Intervention = 12 months; follow-up = 60 months
Patients included in the study	170 after resection of oral leukoplakia
End points	Recurrences of leukoplakias and occurrence of new leukoplakias and cancer
Results	Protective effect of fenretinide
Remarks	The protective effect lasted significantly for 7 months after drug interruption

HNSCC head and neck squamous cell carcinoma, *DFS* disease-free survival

no protective effect was shown [84, 85, 88, 89]. The toxicity of etretinate is very high and many patients enrolled in the French study [84] discontinued treatment because of the side effects. The toxicity of high-dose isotretinoin was observed in all of the studies and its severity required many patients to discontinue therapy [83, 90–92]. On the contrary low-dose isotretinoin was well tolerated and was more effective than β -carotene. Several studies tested the effectiveness of another synthetic retinoid, N-(4-hydroxyphenyl) retinamide (fenretinide or 4-HPR) in preventing the clinical progression of oral leukoplakia via receptor-independent apoptosis and receptor-dependent effects [67, 93, 94]. These studies showed that fenretinide is a well-tolerated drug, able to prevent new occurrences of oral leukoplakias without improved efficacy at higher doses [93, 94]. After interruption of the pharmacotherapy, however, the protective effect of retinoids decreases over time and some patients can develop new leukoplakias and squamous cell carcinomas [66, 94]. In the Hong study [66, 83], the difference between the odds ratio of developing a second primary tumor at any site for isotretinoin-treated group diminishes over time and no statistically significant difference in survival has been observed. In the Chiesa study [67], the protective effect of fenretinide was shown to last significantly for 7 months after the completion of a 1-year intervention.

cancer of the upper aerodigestive tract because of lack of micronutrients and vitamin A in their diet, or of heavy alcohol and tobacco use. Intervention generally lasted several years and the results in term of reduced mortality from or reduced incidence of cancer were evaluated for at least 5 years after the end of the interventions. Table 2.3 shows the results of these trials [96–104]. Retinoid and micronutrient supplementation showed a protective effect in populations with low tissue levels of retinoids, but it was dangerous in individuals with normal retinoid levels, inducing a higher incidence of cardiovascular diseases and lung cancer. Two studies were stopped because of these results [98–103]. A relationship between lung cancer and serum levels of some carotenoids seem to show some gender predilection favoring males, with no apparent association observed among women [105]. These results and a critical review of the literature allow us to conclude that there is no evidence to support antioxidant supplementation for primary or secondary prevention, while Vitamin A, β -carotene, and Vitamin E may increase mortality [106–108]. Future randomized trials could evaluate the potential effects of Vitamin C and selenium for primary and secondary prevention with close monitoring for potential harmful effects. Antioxidant supplements need to be considered medicinal products and should undergo sufficient evaluation before marketing [109].

Chemoprevention in High-Risk Populations

This form of chemoprevention consists of dietary supplementation with vitamins, retinoids, and micronutrients in high-risk populations. During the final two decades of the last century several preventive studies have been conducted all over the world (China, Scandinavian countries, USA) [96, 97]. These trials included thousands of patients at risk for developing a

New Directions in Chemoprevention

Following the conflicting and intriguing results of the early chemoprevention trials, other therapeutic regimens (single drug or combination) have recently been evaluated [95, 110–115]. Most studies tested anti-inflammatory drugs, including COX-inhibitors and aspirin, because of the strong link between nonsteroidal anti-inflammatory drugs (NSAIDs) and the

Table 2.3 Chemoprevention trials in high-risk populations

<i>Blot WJ, 1993 [96]</i>	
Design	Diet supplementation with Retinol + zinc (Group A), riboflavin + niacin (Group B), Vitamin C + molybdenum (Group C), β -carotene + Vitamin E + selenium (Group D)
Length of the study	Diet supplementation = 5 years; follow-up = 2 more years
Patients included in the study	29,584 at risk for esophageal and gastric cancer
End point	Decrease of mortality for esophageal, and stomach cancer
Results	Significantly lower mortality for cancer was found in group D, evident after 1–2 years
Remarks	No significant effect on mortality rates for all causes was found in the other arms
<i>Li JY, 1993 [97]</i>	
Design	Diet supplementation with 12 minerals + 14 vitamins vs. placebo
Length of the study	6 years
Patients included in the study	3,318 subjects with esophageal dysplasia
End point	Decrease in cancer mortality and incidence
Results	No substantial short-term beneficial effect on incidence or mortality for esophageal cancer
Remarks	Cancer mortality 4% lower (RR = 0.96) and cerebrovascular disease 38% lower (RR = 0.62) in intervention group, not statistically significant
<i>ABTC Study Group, 1994 [98], Albanes D, 1996 [99], Virtamo J, 2003 [100]</i>	
Design	α -Tocopherol (50 mg/day) (Group I), β -carotene (20 mg/day) (Group II), both (Group III), placebo (Group IV)
Length of the study	5–8 years (Median 6.1 years)
Patients included in the study	29,153 Male Finnish, 50–69 years old, smokers ≥ 5 cigarettes/day
End point	Reduction in lung cancer incidence
Results	Multicentric study Higher incidence of lung cancer and ischemic heart disease in those receiving β -carotene No reduction in lung cancer in those receiving α -tocopherol
Remarks	Fewer prostate cancers, but more deaths from hemorrhagic stroke in the α -tocopherol group The beneficial and adverse effects of supplemental α -tocopherol and β -carotene disappeared during postintervention follow-up
<i>Omenn GS, 1996 [101, 102], Goodman GE, 2004 [103]</i>	
Design	β -Carotene 30 mg/day + Vitamin A 25,000 IU vs. Placebo
Length of the study	4 years (stopped 21 months early than planned)
Patients included in the study	18,314 smokers, former smokers and workers exposed to asbestos
End point	Decrease in lung cancer incidence
Results	Multicentric study Stopped due to higher incidence of lung cancers (RR = 1.28) and death for lung cancer (RR = 1.46) and for cardiovascular diseases (RR = 1.26) in the intervention group as compared with the placebo group The adverse effects persisted after supplementation was stopped (as of December 2004), although not statistically significant
<i>Lin J, 2009 [104]</i>	
Design	Vitamin C Group (ascorbic acid 500 mg/day), vitamin E group (α -tocopherol 600 IU/every other day), β -carotene group (50 mg/every other day), placebo
Length of the study	9.4 years (average)
Patients included in the study	7,627 women free of cancer before randomization
End point	Incidence and death from cancer
Results	No overall benefits in the primary prevention of total cancer incidence or cancer mortality
Remarks	Multicentric, double-blind, placebo-controlled $2 \times 2 \times 2$ factorial trial

reduction of cancer incidence demonstrated in human epidemiological studies. The NSAIDs family inhibits the cyclooxygenase (COX) family of enzymes. COX-2 has been shown to be upregulated as much as 150-fold in HNSCC and 50-fold in the normal appearing tissue of patients with HNSCC compared with normal subjects [116]. However, problems and results of the first multicentric studies using these agents are similar to those obtained with the retinoids [117–120]. Heath et al. [117] found that administration of 200 mg of celecoxib twice daily for 48 weeks of treatment

does not appear to prevent progression of Barrett's dysplasia to cancer. In a hospital-based case-control study (529 patients with HNSCC vs. 529 controls), Jayaprakash et al. concluded that aspirin use reduces the risk of HNC (25%; OR 0.75) [119]. This effect is more pronounced in women and in individuals with low to moderate exposure to cigarette smoke or alcohol consumption. Heavy smokers and alcohol drinkers did not benefit from the protective effect of aspirin.

Current basic science advances are swiftly followed by an inability to translate them into clinically relevant interventions,

to verify end-points and to establish adequate follow-up. As of September 2009 the National Institute of Health [120] reports six recruiting chemoprevention clinical trials using molecular agents (kinase or serine protease inhibitors), and anti-inflammatory drugs (COX-2 inhibitors, sulindac, or acetylsalicylic acid) as single agents or in combination. In addition to these, 11 other primary or adjuvant chemoprevention trials are currently active, but not yet in the recruiting phase: their purpose is to test the effectiveness of natural and synthetic retinoids (four trials), dietary supplementation (one study), anti-inflammatory (four studies), and antidiabetic drugs (two studies).

Chemoprevention trials are expensive because of the large study population needed and the necessary length of the studies. Cost analysis of these trials includes the sample size, the total number of study subjects and the necessary lengthy follow-up, the number of trial outcomes evaluated, possible delays in the accrual process, and cost effectiveness of particular retention activities. Based on the negative experiences made with the CARET study, the psychological effects of information relating to possible negative outcomes of the study (involving healthy population) should also be considered [121, 122].

The original promise HNC chemoprevention will be fulfilled only if putative biomarkers are validated with well designed and adequately funded long-term studies, that allow the creation of accurate molecular risk stratification models and translate into significant changes to clinical practice [17, 81, 93, 123, 124].

Prevention of Neck Metastases

One of the basic issues of secondary and tertiary prevention in HNC is linked to the possibility of prevention of neck metastases [125, 126]. The neck is the central point in the management of HNSCCs; once metastases become clinically apparent, extra-capsular spread (ECS), a known prognostic factor [125, 126, 132], is more likely than in occult metastatic disease where ECS is estimated to be more than 15–20% [126–128]. ECS does not depend on the quantity of tumor cells present in the metastatic nodes: up to 60% of micro-metastatic nodes (cN0 pN1) show ECS [129–131]. A study by Woolgar evaluating the treatment results in a series of patients with head and neck cancer [128] showed that, regardless of the T stage, the overall survival (OS) depends upon the pathological lymph node status: OS in pN0 patients was 73%, in pN+ without ECS=51%, and in pN+ with ECS was 29%. Distant metastases and local recurrences are also significantly related to the lymph node status [132]. Currently, the only specific predictive factors of lymph node metastases are the site, size, and thickness of the primary tumor [130, 133].

Identification of factors affecting invasion and metastasis, as well as the establishment of biomarkers to predict malignant potential and to identify different risk groups are of paramount importance. Cancer cell invasion and metastasis are a complex, multistep process involving interactions between invading cells, the extracellular matrix, and other stromal elements. In the initial phases of tumor progression, tumor cells undergo genetic changes, providing proliferative advantages such as the ability to resist growth-inhibiting signals, avoidance of programmed cell death (apoptosis), induction of blood vessel growth (angiogenesis), loss of cell adhesion and migration, lymphatic angiogenesis, and the ability to survive in the environment of the metastatic site [134–136]. When these metastatic capacities are acquired (early or late) in tumor progression remains unclear, however there is evidence suggesting, in contrast to common belief, early acquisition of this transformation [136]. Many of these competitive advantages may also vary in time. For example, cell adhesion should decrease to allow cells to migrate and metastasize, but cell adhesion is again needed to settle at the metastatic site [134].

Search for Additional More Sensitive Markers

Many biomarkers have been studied to establish correlation with the presence of nodal metastases in HNSCC with widely varying results and include matrix-metalloproteinases (MMP) [134, 137–145], podoplanin [63, 64], p27, ki-67 [146–148], and vascular endothelial growth factor (VEGF) [149, 150]. Recently, new techniques centered upon gene-expression profiling and comparative genomic hybridization with microarray technology have been developed and have allowed reliable detection of predictors of behavior rather than single markers [134, 151–156]. The findings of these studies indicate that these markers identify a subset of patients with poor prognosis, requiring aggressive treatment modalities, including new molecular targeted therapies likely to act as anti-invasion and antimetastatic therapeutic agents [157].

HPV Infection

The HPV is part of a very heterogeneous family of viruses. It represents an important human carcinogen, causing the vast majority of cervical and anogenital tumors, and a variable number of cancers in other districts of the human body including the head and neck [158, 159]. HPV-positive SCCHN have been reported to share some epidemiological and biological characteristics with anogenital carcinomas [160, 161].

Risk Factors for HPV Infection, Oral, and Oropharyngeal Squamous Cell Carcinomas

HPV infection is thought to precede the development of an HPV-positive HNSCC. The presence of high-risk HPV infection in oral mucosa and seropositivity increases significantly the risk of development OSCC [162–166]. Therefore, risk factors for HPV oral infection are likely, by extension, to be risk factors for HPV-positive HNSCC. Patients with HPV-positive tumors appear to be distinct from HPV-negative patients. There is no gender predilection, patients are often nonsmokers and nondrinkers [167, 168] and younger than HPV-negative tumors [169]. The degree to which oral HPV infection may combine with tobacco and/or alcohol use to increase risk of cancer is unclear [160, 169]. In the majority of the studies OSCC related to HPV infection have a better outcome and a reduced risk of relapse and second tumors as compared with HPV-negative tumors [160, 170, 171].

Vaccination as a Form of Prevention

Vaccines designed strictly for prevention of cervical cancer and vulvar genital warts have recently been introduced. The existing vaccines are able to create a robust humoral immune response [172, 173] that is much more effective than the levels of antibodies acquired after a natural infection, and persist at least for a 60-month period [172]. Five-year follow-up demonstrates 100% effectiveness in prevention of persisting infection as well as HPV-16 and HPV-18 CIN 2/3 lesions in young women [173].

HPV-16 is found in the majority of HPV-positive oral cancer [173]. All vaccine trials reported to date have been designed to investigate the ability to generate protection against anogenital HPV infection in women. There is reason to believe that the existing vaccines may be effective against oral HPV infection, and prevent vaccine-type HPV-related HNC in both men and women [172, 174]. Data also suggests that therapeutic vaccines are effective against low-volume disease and could be used as adjuvant therapy following surgery or radiotherapy to clear microscopic residual disease [4]. Clinical trials to evaluate the efficacy of the quadrivalent HPV vaccine (against HPV 6, 11, 16, 18) in protecting against oral infection are currently being developed.

Conclusions

Improvement in the field of prevention requires a multidisciplinary approach. The development of cancer is a complex process, and multiple factors may be crucial in prevention.

A clear geographic variability in cancer risk and burden exists across countries and specific interventions are required in each region. Primary prevention is considered the best form of prevention. Implementation of a primary prevention program requires knowledge of the specific risk factors (tobacco, alcohol, HPV infection) and the ability to limit exposure and to remove them. Efforts to promote healthy lifestyle practices such as tobacco control and cessation programs, recommendation for dietary modification (including alcohol consumption reduction) and weight control have yielded mixed results without significant reduction in the incidence of new cases of HNSCC [41, 175]. This observation highlights the fact that achieving primary prevention is very difficult and has given greater relevance to secondary prevention. Early detection and diagnosis entails by definition the discovery of preneoplastic lesions and early carcinomas. Precancerous lesions and cancer are part of a clinical continuum making it difficult to define where one ends and the other begins. Consequently, it becomes difficult to definitively state what represents therapy for one end of the disease spectrum versus the other [157, 176]. Genetic aberrations do not always result in visible lesions and a large portion of all preneoplastic lesions remains clinically silent. Even recognizing preneoplastic alterations, currently there is no sufficient evidence suggesting that the surgical treatment of precancerous lesions reduces the incidence of cancer [41].

The rapid development of molecular biology, the identification of the fundamental cancer genes and signaling pathways, and the development of new functional diagnostic imaging techniques show renewed promise for early prevention. The stratification of patients in different subgroups based on etiology, genomic classification, and other parameters clearly has important implications. Other than showing promise, however, we have not been able to translate this new knowledge into clinically successful strategies for early detection or chemoprevention of cancer. We are again at the dawn of a new era with the conclusion of the Human Genome Sequencing Project and advances in molecular and cellular pathophysiology hold yet more promise that a deeper understanding of the fundamental disease mechanisms may result in improved prevention and cure. The challenges remain in the correct interpretation of these findings and in their wise and scientific application. Only then will we be able to impact the field of HNC, transforming prevention into the only form of cure.

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