Oral Oncology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Commentary

A local mechanism by which alcohol consumption causes cancer

Miguel López-Lázaro *

Department of Pharmacology, Faculty of Pharmacy, University of Seville, Spain

ARTICLE INFO

Article history:
Received 29 September 2016
Accepted 3 October 2016
Available online xxxx

Keywords:
Alcohol
Cancer
Ethanol
Tobacco
Synergism
Carcinogenesis
Oral cavity
Pharynx
Esophagus
Stem cells

ABSTRACT

Epidemiological data indicate that 5.8% of cancer deaths world-wide are attributable to alcohol consumption. The risk of cancer is higher in tissues in closest contact on ingestion of alcohol, such as the oral cavity, pharynx and esophagus. However, since ethanol is not mutagenic and the carcinogenic metabolite of ethanol (acetaldehyde) is mostly produced in the liver, it is not clear why alcohol use preferentially exerts a local carcinogenic effect. It is well known that ethanol causes cell death at the concentrations present in alcoholic beverages; however, this effect may have been overlooked because dead cells cannot give rise to cancer. Here I discuss that the cytotoxic effect of ethanol on the cells lining the oral cavity, pharynx and esophagus activates the division of the stem cells located in deeper layers of the mucosa to replace the dead cells. Every time stem cells divide, they become exposed to unavoidable errors associated with cell division (e.g., mutations arising during DNA replication and chromosomal alterations occurring during mitosis) and also become highly vulnerable to the genotoxic activity of DNA-damaging agents (e.g., acetaldehyde and tobacco carcinogens). Alcohol consumption may increase the risk of developing cancer of the oral cavity, pharynx and esophagus by promoting the accumulation of cell divisions in the stem cells that maintain these tissues in homeostasis. Understanding the mechanisms of carcinogenicity of alcohol is important to reinforce the epidemiological evidence and to raise public awareness of the strong link between alcohol consumption and cancer.

Introduction

Epidemiological evidence strongly suggests that moderate to heavy alcohol consumption increases the risk of cancer of the oral cavity, pharynx, larynx, esophagus, liver, colon, rectum and female breast [1–3]. Recent estimates indicate that the relative risk for heavy drinkers compared with nondrinkers and occasional drinkers is 5.13 for oral and pharyngeal cancer, 4.95 for esophageal cancer, 2.65 for laryngeal cancer, 2.07 for liver cancer, 1.44 for colorectal cancer and 1.61 for breast cancer [3]. Light alcohol drinking (up to one drink per day) increases the risk of cancer of the oral cavity, pharynx, esophagus and breast, but not of the liver, larynx, colon and rectum [4]. It has been estimated that 5.8% of cancer deaths world-wide are attributable to alcohol use [5]. However, the biological mechanism by which alcohol causes cancer is unclear [1,2,6,7]; this is often raised as an objection to accept the strong epidemiological link between alcohol consumption and cancer [2].

Cancer is caused by exposure to mutagenic agents, but ethanol is not mutagenic. Most of the ingested ethanol is metabolized in the liver to the mutagenic agent acetaldehyde, which reaches the general circulation and is considered to be responsible for the carcinogenicity of alcohol. It is not clear, however, why alcohol use increases the risk of some cancers and not others [1,2,6,7]. The breast cancer risk can be explained by the increased levels of estrogens observed after alcohol consumption; estrogens play an important role in breast carcinogenesis [8]. However, since acetaldehyde is mostly produced in the liver, it is not clear why light alcohol consumption increases the risk of cancer of the oral cavity, pharynx and esophagus but not of the liver and other organs. Epidemiological studies have consistently shown that alcohol consumption causes a local carcinogenic effect. Researchers assessing differences in the carcinogenicity of alcohol on subsites of the head and neck have observed a high risk for anatomical sites in closest contact on ingestion of alcohol, such as the mobile part of the tongue and the hypopharynx [1]. Variations among tissues in the levels of isoenzymes involved in ethanol detoxification (i.e., alcohol dehydrogenases and aldehyde dehydrogenases) cannot explain the local carcinogenic effect of alcohol in individuals with functional isoenzymes [1]. Currently, the biological mechanism by

* Corresponding author at: Department of Pharmacology, Faculty of Pharmacy, University of Seville, C/ Profesor Garcia Gonzalez 2, 41012 Sevilla, Spain.
E-mail address: mlopezlazaro@us.es
URL: https://orcid.org/0000-0003-2794-1647

http://dx.doi.org/10.1016/j.oraloncology.2016.10.001
1368-8375/

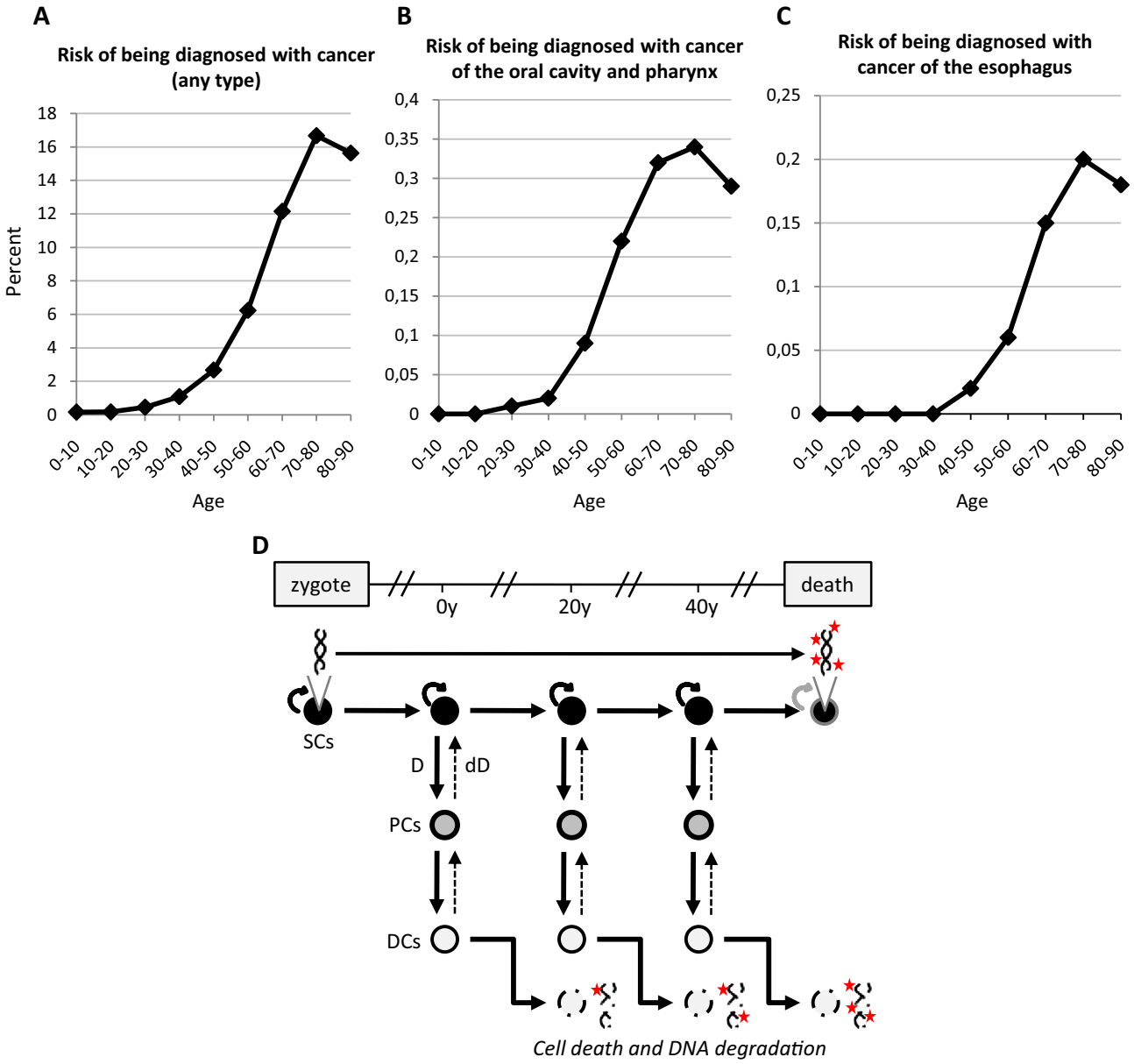

Fig. 1. Cancer risk by age indicates that cancer originates in stem cells. Like for most cancers (A), the risk of being diagnosed with cancer of the oral cavity and pharynx (B) and esophagus (C) increases dramatically with age [11]. This implies that most cancers are the end-result of several successive cellular changes; if cancer were caused by only one cellular change, this change could occur at any moment in life and cancer incidence would be rather similar at different ages [13]. Importantly, DNA is the only cellular component that can accumulate changes throughout life, and stem cells are the only cells that can keep our DNA from the beginning of life (zygote) until death (D). At different moments in life, stem cells pass a copy of our DNA to progenitor cells (transit amplifying cells), which in turn pass it to the differentiated cells that form the bulk of the tissues. However, these DNA copies are degraded when differentiated cells die to be replaced by new cells. As we progress from zygote to death, our stem cells acquire DNA changes that increase our risk of cancer. If cancer originated in non-stem cells, progenitor cells or differentiated cells created at age 0, 20 or 40 would have the same probability of acquiring the first cancer-related change. After a period of e.g. 30 years (during which the cell would acquire the rest of the cancer-related changes required for carcinogenesis), cancer incidence would be rather similar at ages 30, 50 or 70. This is incompatible with cancer statistics shown in panels A–C, even considering the dedifferentiation potential of progenitor and differentiated cells. Therefore, the marked increase in cancer incidence with age indicates that most, if not all, cancers originate and largely develop in stem cells. The known decline in stem cell functionality with age occurring in most tissues [26] can explain why cancer risk decreases late in life. See Ref.[16] for additional details. Curved arrows represent self-renewal capacity. Broken arrows represent less-favored pathways. Stars represent DNA alterations. SCs: stem cells; PCs: progenitor cells; DCs: differentiated cells; D: differentiation; dD: dedifferentiation. Figure adapted from Ref.[16].

which alcohol consumption imposes a high risk of cancer of the oral cavity, pharynx and esophagus remains to be elucidated.

Discussion

Exposure to mutagenic agents is an important cause of cancer; for example, tobacco use is a mutagenic factor that increases the risk of oral cavity cancer and pharyngeal cancer by about 5–10 times [9]. However, ageing and the self-renewal capacity of tissues increase the risk of cancer much more than any known mutagenic agent [10]. The risk of being diagnosed with cancer of the oral cavity and pharynx is about 80 times higher for people over 60 years old than for people under 30 [11]. In addition, tissues with a high self-renewal capacity give rise to cancer even a million times more often than tissues without this capacity [12]. Recent analyses of the stinking differences in cancer risk by age and among tissues indicate that the main biological cause of cancer is the accumulation of cell divisions in stem cells [12–16]. The marked increase in

Please cite this article in press as: López-Lázaro M. A local mechanism by which alcohol consumption causes cancer. Oral Oncol (2016), http://dx.doi.org/10.1016/j.oraloncology.2016.10.001