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Dairy animals and breast cancer: reflections on a long-term study from the 1970s that was never done

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Research Reflection

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Abstract

In this short commentary I recall a long-term experiment that was sketched out to determine if the low incidence of mammary cancer in dairy animals reflects a low incidence in these species generally or is the result of a protective effect of early pregnancy and long lactations. Although that experiment was never done, I discuss these questions in the light of developing knowledge on the incidence of cancer in ruminants generally and in the mammary gland in particular.

In 1971 two American dairy scientists, Stuart Patton (1920–2017) of Penn State University and Robert Jenness (1917–1998) of the University of Minnesota, persuaded the organisers of the Gordon Research Conferences to hold meetings on the 'Biology of Milk'. They intended, and succeeded, in pulling together those interested in milk and mammary glands from a variety of backgrounds including dairy science, fundamental physiology and biochemistry, nutrition, breast feeding and breast cancer. After the third meeting in 1975, the title was changed to 'Mammary Gland Biology'.

It was at the Gordon Conference in 1977 that I was talking to Pietro Gullino (1919–2001). At the time he was Chairman of the U.S. Breast Cancer Task Force while working in the National Cancer Institute of the National Institutes of Health. The conversation turned to other species and the extremely low incidence of mammary cancer in dairy cows and goats.

In 1940, Swett, Matthews and Graves at the US Department of Agriculture in Beltsville, Maryland, published work on the dairy cow. Whole udders were fixed by filling the glands with formalin *via* the teat canals. No sign of mammary cancer was found in the udders of 313 cows of 'lactating age', nor of 105 heifers and freemartins, after extensive examination of thick and thin sections. Swett *et al.* (1940) realised that cows are usually culled from a herd before old age but, by relating cow age to human age in terms of longevity and age at puberty, produced a table showing the equivalent human age of the cows they had studied. By that reckoning nearly 40% of the cows had reached an equivalent human age of 40. Since the incidence of breast cancer increases after that age, they argued, their results still demonstrated a true difference in the incidence of mammary cancer between women and cows.

Reports in the literature of mammary tumours in dairy animals remain very few. One possible explanation is that cows and goats typically become pregnant soon after puberty and then spend most of their artificially shortened lives producing milk. In other words, it is the protective effects of early pregnancy and long lactations together with being culled before tumours have developed that is responsible for the reported low incidence. The obvious question then is: would dairy cows or goats left unmated for their entire lives still show a low incidence of mammary cancer? An entirely different reason could be that cows and goats of all ages have a low incidence of cancers anywhere in the body.

The 1970s was a period of interesting findings in the epidemiology and pathology of human breast cancer. Brian MacMahon (1923–2007) at Harvard had led a major study which showed, as suspected earlier, a positive correlation between the incidence of breast cancer and the age of first pregnancy. Earlier epidemiological findings done first by Janet Elizabeth Lame-Claypon (1877–1967) in London also suggested a protective effect of lactation. In pathology the findings of Andrew Tawse Sandison (1923–1982) working in Glasgow on human breasts obtained at autopsy had been followed up by Hanne Jensen and Sefton Robert Wellings (1927–2011) in the University of California at Davis. A higher incidence of anomalous structures, called 'preneoplastic lesions' was observed in breasts containing cancers compared with the contralateral, non-cancerous breasts of individuals (Jensen *et al.*, 1976). There was also a marked increase in incidence with age. The burning question of the day, namely, whether these 'preneoplastic lesions' really are the precursors of fully transformed breast cancers and whether they are homologous to the 'hyperplastic alveolar nodules' described in mice and which appear to be an important stage in cancer development in that species, the now classical 'model' for breast

cancer (see Medina, 2010) need not concern this discussion, other than to note the very high incidence of these 'preneoplastic lesions' found in very old women.

It was this latter finding in the breasts of old women that appeared to offer the possibility of answering the question as to whether the mammary glands of old dairy animals show what are/were thought to be the precursors of breast cancer. The hypothetical study Pietro Gullino and I sketched out was to keep a herd of unmated female goats, which would have received no possible protection afforded by early pregnancy or lactation, from birth until death (or age-related euthanasia) and then examine their mammary glands for the presence of anomalous structures, like the 'preneoplastic lesions' described in women or the 'hyperplastic alveolar nodules' found in mice, and for tumours of any kind. We knew it would be pointless just looking for obvious cancers since the number of animals required would have been too large. Given that high incidence of 'preneoplastic lesions' in aged human breasts, the number of animals needed for comparison would have been manageable (we guessed 50–100). The longevity of goats is given as 9–18 years but the range usually accepted by goat keepers is 10–12 years. To cut a longer story short, the study was never done; it remained a pipe dream.

It is now only possible to speculate on whether the results would have proved useful. That is because there is accumulating but sometimes conflicting evidence that the incidence of cancers of all tissues is very different in the various mammalian clades. For example, evidence has recently been published (Vincze *et al*., 2021) that the mortality from cancer of non-domesticated ruminants kept in zoos for their entire lifetime is very low in comparison with many other mammals, the Carnivora for instance. In some ruminants, with samples comprising several hundred individuals, the number of deaths from cancer was zero. However, such low rates may not apply in all species or domesticated forms. For example, Löhr (2013) reported 8.7% of 1146 domestic goats sent for autopsy in Oregon had tumours. Seven goats were found to have mammary adenocarcinomas. In the case of the mammary gland, the case reports compiled by Munson and Moresco (2007) which imply a zero incidence of mammary tumours in goats, were incomplete. Prpar Mihevc and Dovč (2013) included earlier findings as well as later data on goats, sheep and cows. The incidence while very low is not zero.

Against this background it could be argued that at one extreme, a presumed low incidence of cancer in ruminants, the study-that-never-happened would have shown no evidence of structures resembling human 'preneoplastic lesions' or murine 'hyperplastic alveolar nodules', nor of fully transformed cancers, in the mammary glands of old virgin goats. It could also be predicted that the absence of mammary cancer in dairy animals is not the result of the protective effects of early pregnancy and long lactations, as in women. However, that may not be the entire story since there is historical evidence that the mammary glands of dairy cows have an even lower incidence of cancer than the organs and tissues of the rest of the body. Swett *et al.* (1940) wrote: '*Feldman in reporting on nearly 13 million bovines slaughtered subject to meat inspection by the Bureau of Animal Industry in 1930, showed that approximately 1300 cases of tumorous growths were found but did not indicate that any occurred in the mammary glands. In fact Creech who reviewed the laboratory findings recorded in a large number of bovine tumors observed in connection with meat inspection activities involving the slaughter of many millions of cattle, over a period of years, has concluded that cancerous growths in the bovine mammary gland are very rare, and that those that have been found apparently originated from carcinoma of the skin and invaded the udder from that source.*'

Perhaps our study would have proved useful, especially had 'preneoplastic lesions' been found in any of the older animals. In that respect, the history of Löhr's (2013) seven goats found to have mammary adenocarcinomas would have been interesting. As the author remarked, '*The high prevalence of tumors in dwarf, Nubian, and Saanen goats could indicate a predisposition of these breeds to neoplastic disease or simply reflect the higher median age of pet (dwarf) and dairy goats compared with goats of other agricultural uses or caprine cases in general*'. There is then the possibility that goats and perhaps cows are more liable to develop mammary cancer if left to live long enough, even if not to the same extent as women, cats or dogs. If that is the case then we are no further forward in answering the questions that were around in the 1970s. So perhaps it is not too late to suggest that somewhere in the world somebody might take up the type of long-term study Pietro Gullino and I mused over 45 years ago.

The greater interest in a comparative approach to mammary cancer evident in recent years is a welcome development. In and beyond the 1970s the emphasis was on finding animals in which the incidence of mammary cancer is high and/or in which oncogenesis could be induced. The aim of the burgeoning cancer research industry was to study cancer in animal 'models' and to find a cure. Questions, of both the 'how' and 'why' kind, have now arisen from the comparative approach as to the reasons why some mammalian groups have a very high incidence of mammary cancer while others, notably artiodactyls, have a very low incidence.

It has gone virtually unrecognised that advances in knowledge of human reproduction and advances in technology have been achieved as a result of work on farm animals funded as part of agricultural research. It is not stretching a point to suggest that studying why dairy animals do not get mammary cancer would yield ultimate benefit to the over two million women in the world diagnosed with breast cancer each year.

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